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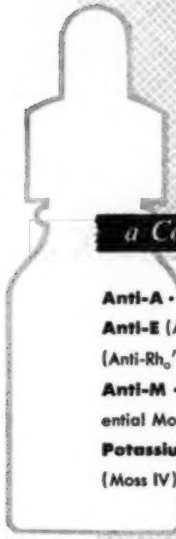

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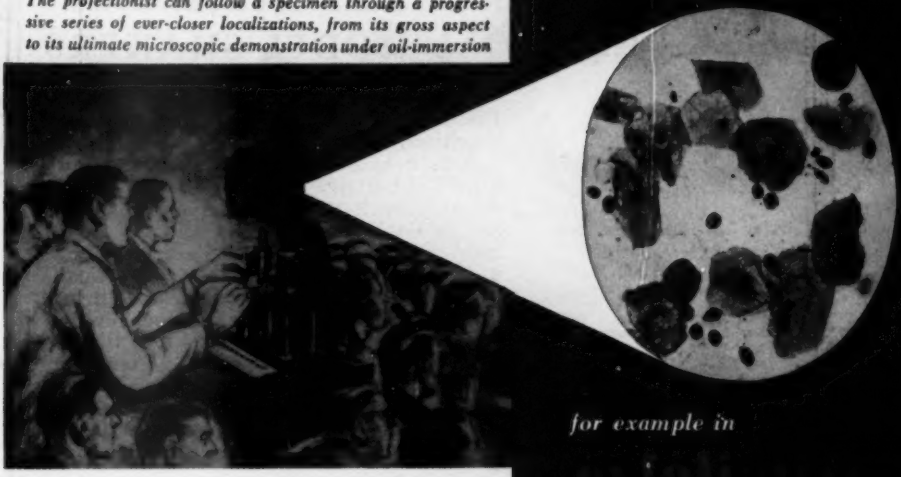

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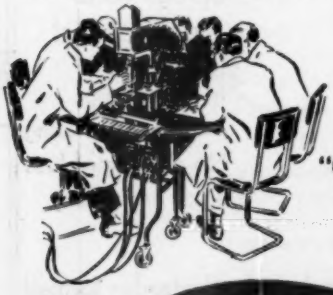

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CONTENTS

PAGE

Diffuse Glomerulonephritis Induced in Rabbits by Small Intravenous Injections of Horse Serum. CHESTER R. MCLEAN, M.D.; JOHN D. L. FITZGERALD, M.D.; OMAR Z. YOUNGHUSBAND, M.D., AND JOHN D. HAMILTON, M.D., KINGSTON, ONT., CANADA 1

Pathogenesis of Experimental Arteriosclerosis in Pyridoxine Deficiency, with Notes on Similarities to Human Arteriosclerosis. JAMES F. RINEHART, M.D., AND LOUIS D. GREENBERG, PH.D., SAN FRANCISCO 12

Effect of Strontium Chloride Feeding on the Rat Molars and Their Supporting Tissues. S. O. BANKS, D.D.S., NASHVILLE, TENN.; S. N. BHASKAR, D.D.S., AND J. P. WEINMANN, M.D., CHICAGO 19

Unilateral Renal Cortical Necrosis and Unilateral Benign and Malignant Nephrosclerosis Associated with Contralateral Renal Artery Occlusion: Report of a Case. STANLEY M. ARONSON, M.D., NEW YORK, AND MARTIN C. SAMPSON, M.D., BRONX, N. Y. 30

Possible Effects of Hypersplenic Extracts on the Hemopoietic Organs of Mice. WILLIAM R. PLATT, M.D., PHILADELPHIA, AND ORVILLE A. ZELLER, B.S., LOUISVILLE, KY. 38

Histologic and Perfusion Studies of the Unmanipulated Kidney in Rabbits with Unilateral Renal Hypertension. JACK FLASHER, M.D.; HUGH A. EDMONDSON, M.D., AND DOUGLAS R. DRURY, M.D., LOS ANGELES 53

CASE REPORTS:

Boeck's Sarcoid of the Thyroid Gland. SAM D. CUMMINS, M.D.; D. H. CLARK, M.D., AND T. H. GANDY, M.D., SHREVEPORT, LA. 68

Acute Myelogenous Leukemia with Giant Cell Carcinoma of Thyroid. PAUL DARON, M.D., AND PHILIP PIZZOLATO, M.D., NEW ORLEANS 72

Intramural Abscess of Stomach (Pneumococcus Type VIII). VICTOR PARSONNET, M.D.; J. STUART FISHLER, M.D., AND GRANT L. SANGER, M.D., VALHALLA, N. Y. 76

Adenocarcinoma of the Testis Occurring in Infants: Report of Two Cases. D. MAGNER, M.D., OTTAWA, ONT., CANADA, AND A. J. S. BRYANT, M.D., REGINA, SASK., CANADA 82

Adenocarcinoma Arising in a Diverticulum of the Female Urethra. JOHN D. HAMILTON, M.D., AND W. B. LEACH, M.D., KINGSTON, ONT., CANADA 90

GENERAL REVIEWS:

Tumors of the Heart: Review of the Subject and Report of One Hundred and Fifty Cases. ROBERT W. PRICHARD, M.D., PHILADELPHIA 98

NOTES AND NEWS 129

OBITUARIES:

WILLIAM F. PETERSEN, M.D. 131

BOOKS RECEIVED 134

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VOLUME 51 JANUARY 1951 NUMBER 1

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DIFFUSE GLOMERULONEPHRITIS INDUCED IN RABBITS BY SMALL INTRAVENOUS INJECTIONS OF HORSE SERUM

CHESTER R. McLEAN, M.D.
JOHN D. L. FITZGERALD, M.D.*
OMAR Z. YOUNGHUSBAND, M.D.*
AND
JOHN D. HAMILTON, M.D.
KINGSTON, ONT., CANADA

IN THE SEARCH for further understanding of the etiology and pathogenesis of glomerulonephritis, numerous technics have been evolved to produce in experimental animals renal lesions resembling those of the human disease. The experimental lesions most closely resembling those in man have been associated almost invariably with some form of an immune reaction of a hypersensitive animal. Of these lesions, the best known is the so-called Masugi nephritis, induced by the injection of "nephrotoxic sera." [1] More recently, Hawn and Janeway,[2] More and Waugh [3] and we [4] have injected intravenously large amounts of bovine gamma globulin to induce diffuse glomerulonephritis of a non-necrotizing, proliferative type. The intravenous injection of such large quantities of foreign serum causes "serum sickness" in rabbits [5] and is associated with the production of acute arteritis, cardiac valvulitis and severe diffuse glomerulonephritis in a high percentage of treated animals.[6]

The purpose of the present report is to describe the results of a relatively simple experimental procedure in which lesions of diffuse glomerulonephritis have been produced in rabbits in the absence of arteritis and cardiac valvulitis by administering small quantities of an antigen during prolonged periods of time.

MATERIALS AND METHODS

Thirty-one albino rabbits formed the experimental series; 18 other animals derived from the same sources and living in the animal house at the same time served as controls. All animals weighed from 2,000 to 2,500 Gm. at the beginning of the experiments. They were fed purina®

From the Department of Pathology, Queen's University.

* Graduate Medical Research Fellow, National Research Council of Canada.

This work was assisted by a grant in aid from the National Research Council of Canada.

1. Masugi, M.: Beitr. z. path. Anat. u. z. allg. Path. **92**:429, 1934. Masugi, M., and Sato, Y.: Virchows Arch. f. path. Anat. **293**:615, 1934.

2. Hawn, C. V., and Janeway, C. A.: J. Exper. Med. **85**:571, 1947.

3. More, R. H., and Waugh, D.: J. Exper. Med. **89**:591, 1949.

4. McLean, C. R.; Younghusband, O. Z.; Fitzgerald, J. D. L., and Hamilton, J. D.: To be published.

5. Fleisher, M. S., and Jones, L.: J. Exper. Med. **54**:55 and 79, 1931.

6. Hawn and Janeway.[2] More and Waugh.[3] McLean and others.[4]

rabbit chow and water ad libitum. Whole horse serum, passed through a Seitz filter and stored in rubber-capped bottles at 4 C. without preservative, was utilized as antigen.

Plan of Experiments.—The experiments were designed to study the histologic effects produced by small daily doses of horse serum injected intravenously over varying periods of time. In order that a study might be made of the evolution and progression of lesions, if any should occur, the experimental series was divided into four groups which were killed at progressively longer intervals ranging from three to 13 months. Unilateral nephrectomy appears to enhance the severity of glomerular lesions produced by one or several large doses of bovine gamma globulin,[7] and this procedure was carried out at some time during treatment on 20 of the 31 treated animals. The experimental series, comprised of three groups of eight and one group of seven rabbits each, were then treated as follows:

Group 1 received 0.5 cc. of horse serum daily for a period of 13 months. Nephrectomy was not performed on this group.

Group 2 received 0.5 cc. of horse serum daily for six months. Left nephrectomy was then performed, and the animals were treated for a further two months as before.

Group 3 received 0.5 cc. of horse serum daily for three months. Left nephrectomy was then performed, and the animals were given serum for a further month.

Group 4 underwent left nephrectomy before receiving any serotherapy. Beginning the day after operation, this group received 0.5 cc. of horse serum daily for three months.

Histological Studies.—At the end of the treatment periods, the animals were put to death by air embolism. Histological sections of brain, thymus, heart, lung, stomach, intestine, mesentery, liver, pancreas, spleen, adrenal, kidney, striated muscle and testis and epididymis, or ovary and uterus, were prepared and stained with hemalum, phloxine and saffron. The kidney sections were also stained according to the Masson trichrome technic.

Serologic Studies.—Precipitin estimations were made on serums from the treated group at monthly intervals. A simple contact ring test was used, employing full strength antiserum and dilutions of antigen. This method is satisfactory for gross estimations of the presence or the absence of antibody. It does not lend itself to even semiquantitative interpretations, because of the multiplicity of antigens present in whole horse serum.[8]

Skin Tests.—Skin tests were performed on the animals of the treated group only. One-tenth cubic centimeter of undiluted antigen was introduced very carefully into the shaved backs of treated animals at monthly intervals. The development, in 12 to 24 hours, of a clearcut area of hemorrhagic tissue necrosis was recorded as a positive reaction (+ +), or Arthus phenomenon. In several animals, necrosis failed to develop, but a wheal appeared, with surrounding erythema, persisting 12 to 48 hours. These reactions were recorded (+), representing a positive skin test but not a completely typical Arthus phenomenon.

Blood Urea Determinations.—Determinations of the blood urea levels were performed just prior to death.

RESULTS

Five animals died during the course of the experiments, or were killed because they appeared critically ill and unlikely to survive. Two additional animals were killed during the performance of left nephrectomy. In all these cases the animals had been treated for a sufficiently long period to provide significant material for histological study.

The periods of treatment, the animals in which left nephrectomy was performed, the incidence of glomerulonephritis in both excised and autopsy kidneys, the blood urea levels, the serum precipitin titers and the skin test reactions are recorded in the table.

Histological Observations.—Definite renal lesions of glomerulonephritis were encountered in 20, or 64.5 per cent, of the 31 treated rabbits. The alterations were

7. More and Waugh.[3] McLean and others.[4]

8. Cannon, P. R., and Marshal, C. E.: J. Immunol. **40**:127, 1941.

Serologic and Anatomic Findings in Relation to Periods of Treatment and Types of Treatment

Animal	Prenephrectomy Treatment Period, Mo.	Left Nephrectomy	Post-Nephrectomy Treatment Period, Mo.	Skin Test Reaction	Terminal Blood Urea, Mg. per 100 Cc.	Highest Serum Precipitin Titer	Renal Lesions of Glomerulonephritis		
							In Kidneys Examined at Autopsy		
							In Surgically Excised Kidneys	Acute Proliferative Glomerulonephritis	Subacute and Chronic Glomerulonephritis
Group 1									
5	13	0	0	++	315	1:1000	..	..	++++
6	10	0	0	++	...	1:100	..	..	++++
7	13	0	0	0	...	0	..	0	0
8	13	0	0	0	33	0	..	0	0
10	11½	0	0	++	...	1:1000	..	..	++++
11	12	0	0	++	328	1:100	..	..	++++
12	13	0	0	++	44	1:100	..	0	0
Group 2									
35	6	+	1	++	...	1:1000	0	0	0
38	6	+	½	++	44	1:1000	0	+	.....
41	6	+	½	++	48	1:1000	0	+	.....
42	6	+	½	++	51	1:1000	0	+	.....
44	6	+	2	+	29	1:1000	0	++	.....
46	6	+	2	+	101	1:1000	0	..	+++
47	5	Died at 5 mo.	0	++	...	1:1000	..	0	0
48	6	+	2	0	56	1:1000	0	++	.....
Group 3									
114	3	+	1	+	34	1:100	0	++	.....
115	3	+	½	+	318	1:100	0	+++	.....
116	3	Died at O. R.	0	0	63	1:100	0	++	.....
117	3	+	1	++	47	1:100	0	+	.....
118	3	+	1	++	57	1:100	0	+	.....
119	3	Died at 3 mo.	0	+	54	1:100	0	..	+++
120	3	+	1	++	40	1:1000	0	0	0
121	3	Died at O. R.	0	+	...	1:100	0	+	.....
Group 4									
45	0	+	3	++	36	1:100	0	0	0
122	0	+	3	++	63	1:1000	0	+++	.....
123	0	+	3	++	39	1:100	0	0	0
124	0	+	3	++	124	1:100	0	++	.....
125	0	+	3	++	44	1:100	0	+	.....
134	0	+	3	++	42	1:100	0	0	0
135	0	+	3	++	30	1:100	0	0	0
136	0	+	3	+	39	1:100	0	0	0
31	..	..	..	....	...	.....	..	14	6

clearly in the nature of diffuse progressive glomerulonephritis and were not at all similar to the occasional foci of spontaneous interstitial nephritis seen in several of the treated and the control rabbits. None of the treated or the control animals had acute arteritis either in the coronary or other visceral arteries. Three blocks of heart muscle were prepared from each animal, and from each of these one to two histological sections were cut. Careful search failed to reveal any of the focal inflammatory lesions of heart valves which have been so frequently described and attributed to the effects produced by one or several large injections of foreign protein in the rabbit.[9] Sections of brain, thymus, lung, stomach, intestine, mesentery, liver, pancreas, adrenal, striated muscle and testis and epididymis, or ovary and uterus, of the treated group failed to show any lesions that could be attributed to the serum injections.

The glomerular changes were readily classified as acute proliferative glomerulonephritis (14 animals) and advanced subacute and chronic glomerulonephritis (6 animals). All the renal lesions in the latter group were of a severe degree and were graded as 3 + to 4 +. They appeared to represent a progression of the acute lesions.

The earliest detectable changes in the glomeruli of the acute proliferative group appeared to involve simultaneously both the epithelial and the endothelial cells of the glomerular capillaries and, to a less degree, their basement membranes. Affected glomeruli appeared appreciably larger than normal but contained less blood than usual. The epithelial cell nuclei were enlarged and vesicular, though not increased in number, and their cytoplasm was unusually conspicuous and redundant, so that the capillary loops often appeared as compressed clefts in a somewhat solid-appearing glomerulus (fig. 1 *D*). The basement membranes of the glomerular tufts frequently exhibited slight degrees of thickening and irregular beading.

While the above alterations appeared to be among the earliest or slightest changes observed in damaged glomeruli, the commonest lesion of the acute group was that of swelling and actual proliferation of capillary endothelium, so that one or more tufts within a glomerulus became narrowed and occluded by the accumulation of cells. Frequently associated with these changes was the presence of small amounts of precipitated protein lying within the capsular space. Increase in size and number of the cells within the mesangium separating contiguous capillary loops contributed to the compression and narrowing of their lumens. In lesions somewhat older and severer, fusion of adjacent capillary loops and the formation of typical epithelial crescents were quite apparent. In the severest degrees of this process the entire glomerulus became involved, all the capillary loops in isolated glomeruli being obliterated and replaced by solid nests of proliferating cells of mixed epithelial and endothelial origin (fig. 2 *C*). In those cases of acute glomerulonephritis in which the glomerular damage was slight, as well as in the cases in which it was severe, the renal tubules showed no changes apart from the presence of small to moderate numbers of hyaline casts in the convoluted and collecting tubules.

The renal lesions which we classified as subacute and chronic glomerulonephritis were of a severe degree in all six animals and represented widespread destruction

9. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **73**:239, 1943. McKeowan, E. F., J. Path. & Bact. **59**:547, 1947. More, R. H.; Waugh, D., and Kobernick, S. D.: J. Exper. Med. **89**:555, 1949.

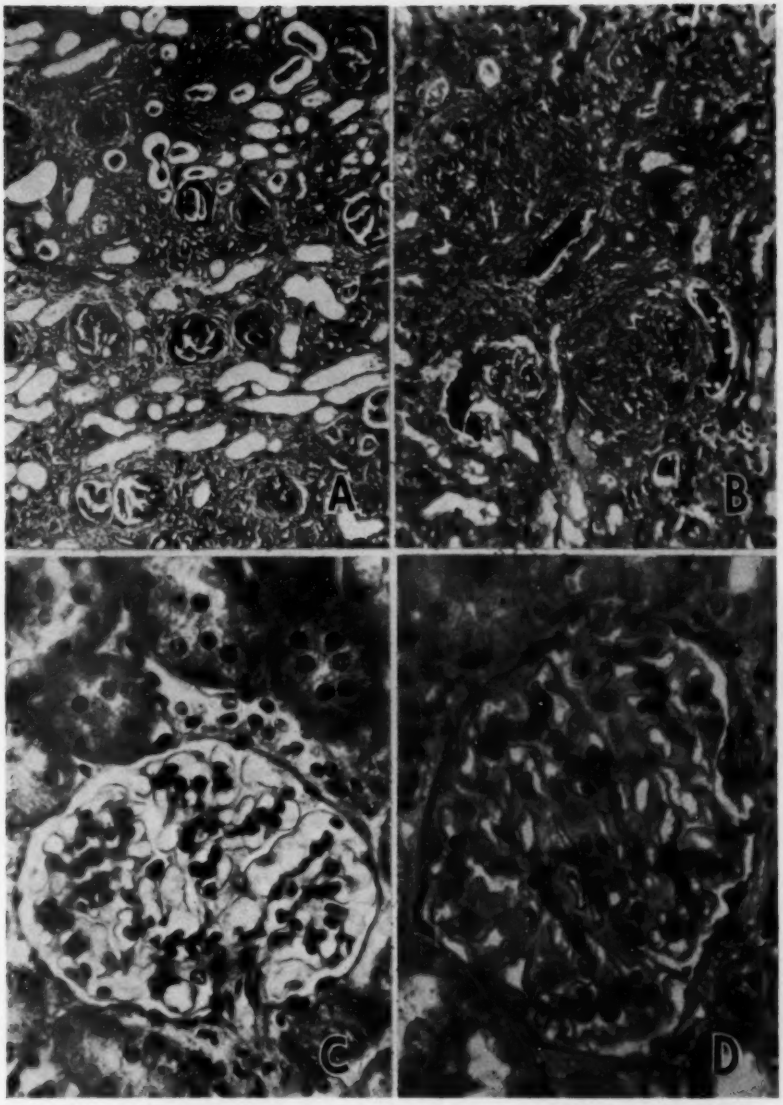

Fig. 1.—*A*, kidney of rabbit that received daily injections of whole horse serum for six months and was then subjected to left nephrectomy, followed by two additional months of serotherapy. It shows diffuse involvement of glomeruli with adherence of capillary tufts and crescent formation. There is marked atrophy of tubules, with dilatation of those that remain. This and figures *2 D* and *3* are representative of the lesions classified as subacute and chronic glomerulonephritis. × 42.

B, kidney of rabbit subjected to left nephrectomy and then treated for three months. The glomeruli are enlarged and show marked proliferation of the capillary endothelium. Crescent formation is clearly seen. The tubules appear normal except for the presence of casts. This and figures 1 *D* and *2* are representative of the lesions classified as acute glomerulonephritis. × 118.

C, normal glomerulus in untreated animal. × 323.

D, glomerulus of rabbit that received daily injections for six months and then was subjected to left nephrectomy and two additional months of serotherapy. The glomerulus appears enlarged and "solid." There is little increase in the number of nuclei, but the cytoplasm of the capillary epithelium is swollen and redundant, reducing the lumens of the capillary loops to irregular clefts. × 430.

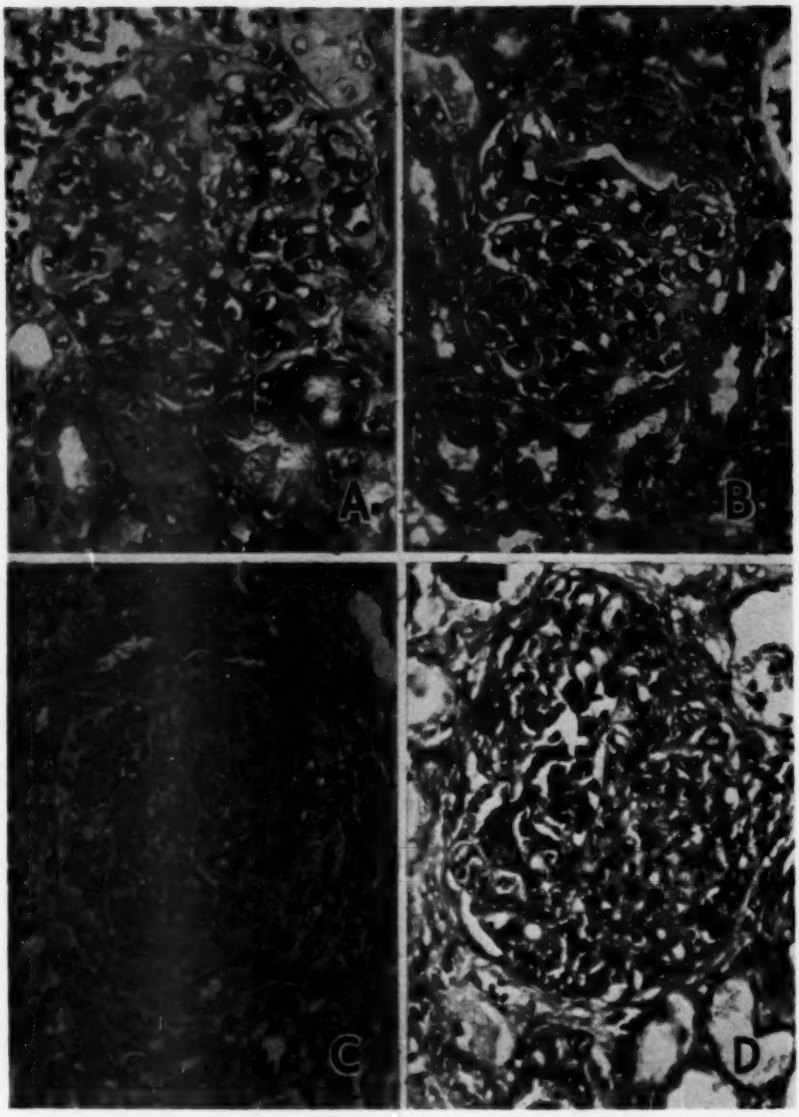

Fig. 2.—*A*, glomerulus from an intact rabbit which received daily serum injections for three months and was then killed accidentally during the performance of left nephrectomy. Many of the capillary loops are partially occluded by swollen, proliferating endothelial nuclei. The capillary basement membranes show marked beading and thickening. × 323.

B, glomerulus of an animal that was nephrectomized and then given daily serum injections for three months. The majority of the capillaries are obstructed by endothelial cells, and a well defined epithelial crescent is present at the upper margin of the glomerulus. × 262.

C, glomerulus from the same kidney as that illustrated in *B*. The endothelial and epithelial proliferation within the glomerulus is of a high degree. × 300.

D, glomerulus of an intact animal which was given serum daily during a 10 month period, at the end of which time it died. The normal glomerular pattern has been replaced by a rather solid mass of proliferating endothelial and epithelial cells. × 218.

of glomeruli and tubules quite compatible with the biochemical findings of renal failure and uremia. Collagen fibers appeared between the capillary loops and around Bowman's capsule, so that adjacent capillary loops became adherent to one another and to Bowman's capsule. Progressive fibrosis both within and around the glomerulus led to complete obliteration of the capillary loops within that structure. In such instances complete atrophy and involution of the associated tubules, or marked dilatation with flattening of the lining epithelium, was the rule. Acute necrotizing lesions of the tubular epithelium were not seen in any instances of either the acute or the subacute and chronic stages. The changes of tubular dilatation, atrophy and cast formation, when found, were always seen in association with severe glomerular damage and probably represented the effects of ischemic atrophy and obstruction due to casts. While interstitial fibrosis was prominent, it appeared to be secondary to the tubular atrophy. Glomerulonephritis was not found in any of the surgically excised kidneys, nor were similar lesions found in the kidneys of any of the control rabbits.

Serologic Findings.—The results of the ring tests are shown in the table. The ratios represent the highest dilutions of antigen with which positive reactions were obtained during the course of treatment. All animals in which glomerulonephritis developed had demonstrable antibodies in their serums. Precipitins appeared in low titers in the majority of the animal serums within a matter of weeks and reached maximum titers of 1:100 and 1:1,000 usually within a period of two months' treatment. The serum titers did not change markedly during the course of the experiment, and there was nothing in the values recorded which could be correlated with the presence or the absence of nephritis. Two rabbits in group 1 (nos. 7 and 8) failed to develop any demonstrable precipitin during the entire treatment period of 13 months. These animals were without renal lesions, and repeated skin tests were also consistently negative. Especial precautions were not taken to protect the animals from the effects of anaphylactic shock. Severe reactions were not encountered, and no animals died of anaphylactic shock during the course of treatment.

Fleisher and Jones [5] have described an "aural flushing" which appears in the ears of rabbits five to seven days after the intravenous injection of foreign protein. This observation has been confirmed [10] and is generally accepted as an index of serum sickness in rabbits. Many animals in the present series underwent one or several episodes of aural flushing during the course of their treatment. The aural changes were quite unmistakable, for the ears became thickened and boggy. The dilatation of small vessels was so great that even in transmitted light the outlines of the larger arteries and veins were obscured by uniform hyperemia, and intravenous injection became quite difficult. These changes have been mentioned in some detail because they are ordinarily recognized as an index of serum disease in rabbits, and acute arteritis frequently accompanies its development. The failure of arterial lesions to develop in these animals may well be due to the small quantity of freely circulating antigen introduced at any one time.

Skin Tests.—Twenty animals exhibited at some time during treatment a typical Arthus reaction following the intracutaneous injection of the antigen. Seven others

10. Hopps, H. C., and Wissler, R. W.: J. Lab. & Clin. Med. **31**:939, 1946.

gave a positive reaction to the skin test, with a wheal and peripheral edema about the site of injection. Four animals, however, failed to give a positive reaction to any of the monthly skin tests performed during their treatment. Two of these also failed to develop demonstrable precipitins, and their kidneys were free of renal lesions. The two remaining animals, however, were noteworthy in that they did have serum precipitins and lesions of glomerulonephritis without ever having demonstrated a positive reaction to the skin test. Thus, of the 20 rabbits with glomerulonephritis, 18 exhibited a positive skin test, while two did not.

Blood Urea Determinations.—The blood urea levels of six of the treated animals were elevated above 75 mg. per 100 cc., and in three of these, exceeded 300 mg. per 100 cc. The degree of renal damage, especially in the latter three animals, appeared to be quite compatible with this degree of renal failure and urea retention. Two animals of group 1 died unexpectedly, and blood urea determinations were not performed. The renal alterations in these rabbits were as severe as any observed in the series, and it is altogether probable that these animals died of renal failure.

COMMENT

Interstitial inflammatory lesions of the kidneys of rabbits arising as a spontaneout disease are well known, and have been attributed by Goodpasture [11] to the organism Encephalitozoon cuniculi. The confusion arising out of failure to identify these lesions in kidneys which form the material of experimental studies has been emphasized in the extensive reviews of Horn [12] and Leiter.[13] Diffuse glomerulonephritis occurring as a spontaneous disease has been observed in mice [14] and rats [15] but has not been recognized as a spontaneous disease in numerous studies on the kidneys of rabbits.[6] The high incidence of diffuse glomerulonephritis (64.5 per cent) in the present series is without doubt related to the serotherapy which the animals received.

The procedure of unilateral nephrectomy may be employed with profit to increase the incidence and severity of glomerulonephritis induced by one or several large injections of foreign serum.[7] Left nephrectomy did not appear to increase the incidence or the severity of the renal lesions caused by daily small injections of serum. The time at which nephritis was liable to occur was unpredictable. In the present series, it was found in a severe form in one intact animal as early as three months after the onset of serum injections.

The renal lesions produced by prolonged administration of small quantities of antigen were histologically very similar to, if not identical with, those of the human disease in virtually all respects. The glomeruli were diffusely and uniformly involved. Proliferative activity of the capillary endothelium was followed by proliferation of the capillary and capsular epithelium, leading to occlusion, compression and relative bloodlessness of the glomerular tufts. This appeared to be the principal

11. Goodpasture, E. W.: J. Infect. Dis. **34**:428, 1924.

12. Horn, H.: Experimental Nephropathies, Arch. Path. **23**:241 (Feb.) 1937.

13. Leiter, L.: Experimental Chronic Glomerulonephritis, Arch. Int. Med. **33**:610 (May) 1924.

14. Kirschbaum, A.: Proc. Soc. Exper. Biol. & Med. **55**:280, 1944.

15. Seegal, B. C., and Loeb, E. N.: J. Exper. Med. **84**:211, 1946.

tissue response which characterized the acute stage. In the over-all picture the changes were quite comparable to the so-called type I nephritis of Ellis, Evans and Wilson.[16]

Ellis, Evans and Wilson pointed out that the ultimate prognosis of type I nephritis is relatively good. All the animals in the present series received serotherapy until killed, and an opportunity for regression of the lesions was therefore not provided. Thus it cannot be stated at this time whether or not the severer degrees of the acute proliferative form of the experimental disease are capable of regression with restitution to normalcy. The older lesions which were classified as advanced subacute and chronic glomerulonephritis appeared to represent acute lesions that had progressed to a stage of extreme glomerular scarring with atrophy of the related tubules. At this stage the lesions most certainly were not capable of resolution. It was not surprising that renal failure and uremia developed in several of the animals exhibiting this histologic picture of advanced renal disease. If edema corresponding to the nephrotic phase of the human disease did occur, it must have been slight, for it was not noted during the course of treatment.

While the great majority of the animals developed serum precipitins and reacted positively to the skin tests during their treatment, two animals remained completely resistant. They did not develop serum precipitins or show a positive reaction to the skin tests during 13 months of daily injections. The kidneys of these animals were free of renal lesions. The immune responses of two additional animals (48 and 116) were also noteworthy in that they developed precipitins and had renal lesions but failed on several successive occasions to exhibit a positive reaction to the skin test. It is well recognized that the development of generalized or visceral lesions of hypersensitivity is correlated in only a general way with the development of skin hypersensitivity and serum precipitins. Generalized and visceral lesions of hypersensitivity induced by a soluble antigen can occur in the absence of skin hypersensitivity, as shown by the results in the above-mentioned animals (48 and 116). This is a much less frequently observed phenomenon and is a further experimental proof that a negative skin test may not be relied on in ruling out the presence of generalized visceral lesions induced by soluble antigens.

Several different experimental procedures employing some variant of a hypersensitivity reaction can cause a diffuse glomerulonephritis closely similar to, if not identical with, that of the human subject.[17] The question has been raised from time to time whether this glomerulitis is actually the result of an antigen-antibody reaction occurring within the kidney itself or the reflection of a more nonspecific reaction. Smadel and Farr [18] have shown that the Masugi form of nephrotoxic nephritis can be inhibited by restricting the daily intake of dietary protein. More and Waugh [3] have suggested that (1) the coagulability and (2) the concentration of the serum protein fractions may be the significant factors which influence the pathogenesis of these renal alterations. Somewhat counter to these suggestions are the recent observations of Sussman and Freed,[19] who have pro-

16. Ellis, Evans and Wilson, cited by Hadfield, G., and Garrod, L. P.: Recent Advances in Pathology, ed. 5, Philadelphia, The Blakiston Company, 1947.

17. Bell, E. T., and Clawson, M. D.: Am. J. Path. **7**:57, 1931.

18. Smadel, J. E., and Farr, L. E.: J. Exper Med. **65**:527, 1937.

19. Sussman, R. S., and Freed, S. Z.: Proc. Soc. Exper. Biol. & Med. **73**:359, 1950.

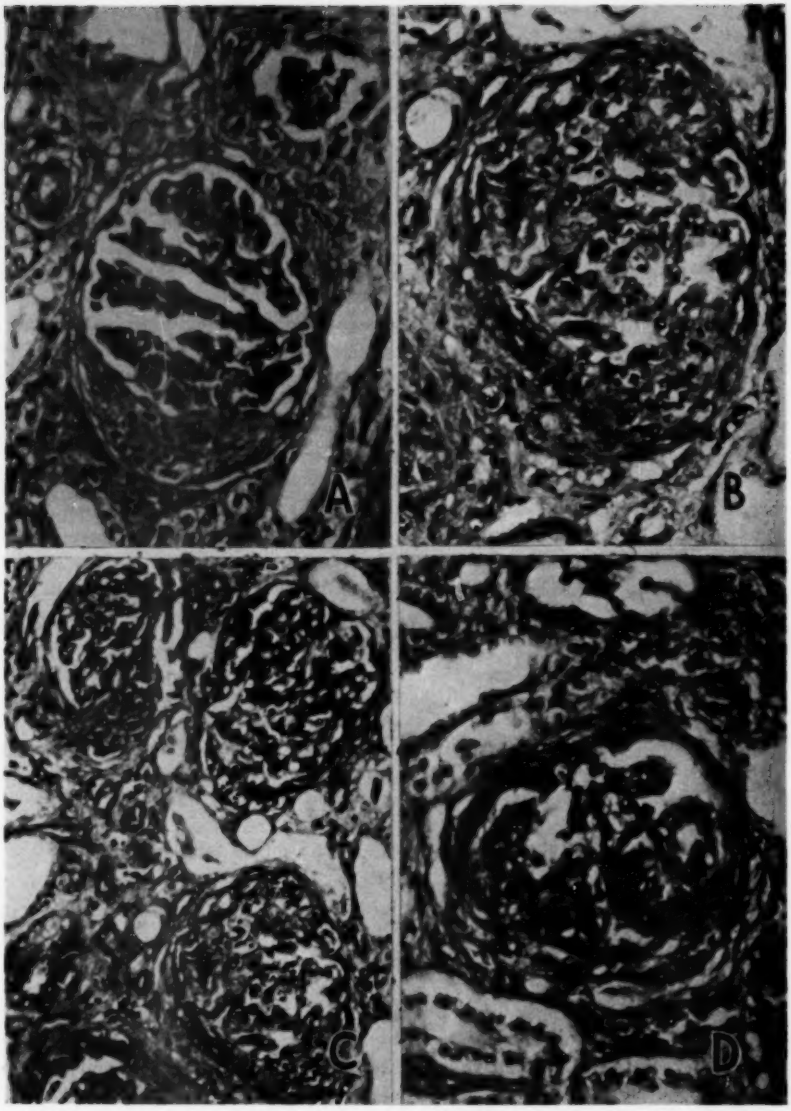

Fig. 3.—*A*, kidney of a rabbit which was treated for three months, then underwent left nephrectomy and received serotherapy for an additional month. There is notable atrophy of tubules and increase of interstitial connective tissue. The glomerulus exhibits a conspicuous crescent. × 243.

B, glomerulus of an intact animal which received daily serotherapy for 10 months, and died. Relatively few patent capillaries are seen within the glomerulus, which also exhibits marked periglomerular fibrosis. × 243.

C, glomeruli from the same kidney as that shown in *B*. The diffuse character of the glomerular involvement is evident. × 213.

D, glomerulus from the kidney illustrated in figure 1 A. Periglomerular fibrosis and adherence of the capillary loops to Bowman's capsule is quite conspicuous. × 213.

duced in rabbits a marked increase in serum gamma globulin, together with a complementary reduction in serum albumin, by intraperitoneal injections of homologous rabbit serum. However, proliferative changes were not observed within the glomeruli of any of these animals, although a few protein coagulums were seen in glomerular capillaries.

In support of the concept that nephrotoxic nephritis is a hypersensitivity reaction, Greenspon and Krakower [20] have produced this form of nephritis by employing, as the original antigen, glomeruli washed free of tubule cells. The specificity of this reaction is shown in the observations of these authors and of Solomon and associates,[21] who have found that glomerular suspensions are capable of absorbing completely the active antibody in nephrotoxic serums. Pressman and Keighley [22] in tracer studies have shown that anti-rat-kidney serum is selectively localized in the kidneys, and in further studies employing autoradiographs, Pressman, Hill and Foote [23] have demonstrated that anti-mouse-kidney serum is quite clearly localized in the glomeruli of treated mice. These experimental conditions are admittedly artificial, but they do constitute good evidence that the kidney is capable of fixing antibodies within itself and responding in a hypersensitive animal with the production of glomerulonephritis very like that of man.

The experimental procedure described in this report has produced similar renal lesions and is submitted as one which may be compared more favorably with conditions that can conceivably obtain in man, that is, prolonged exposure to small quantities of an immunizing antigen. The renal lesions which have been produced have occurred in the absence of acute arteritis and cardiac valvulitis, and thus they fit the criteria of a single morphologic diagnosis and disease entity.

SUMMARY

Thirty-one albino rabbits were treated with small daily injections of whole horse serum for periods of time ranging from three to 13 months. Unilateral nephrectomy was performed on 20 of the animals at some time during the course of treatment.

Diffuse glomerulonephritis was found in 20 (or 64.5 per cent) of the treated animals. In morphologic appearance the experimentally induced lesions bore an impressive resemblance to the renal lesions of human glomerulonephritis.

The renal lesions were progressive in character in that they passed through acute, subacute and chronic phases, with eventual scarring and atrophy, and with renal failure and urea nitrogen retention progressing to levels which in man are considered uremic.

The most significant result of this experimental procedure was the finding of glomerulonephritis in the absence of other lesions attributable to hypersensitivity. Necrotizing arteritis and cardiac valvulitis, which are frequently seen in rabbits treated with large doses of foreign protein, were not observed under the conditions of this experiment.

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20. Greenspon, S. A., and Krakower, C. A.: Direct Evidence for Antigenicity of Glomeruli in Production of Nephrotoxic Serums, Arch. Path. **49**:291 (March) 1950.

21. Solomon, D. H.; Gardella, J. W.; Fanger, H.; Dethier, F. M., and Ferrebee, J. W.: J. Exper. Med. **90**:267, 1949.

22. Pressman, D., and Keighley, G.: J. Immunol. **59**:141, 1948.

23. Pressman, D.; Hill, R. F., and Foote, F. W.: Science **109**:65, 1949.

PATHOGENESIS OF EXPERIMENTAL ARTERIOSCLEROSIS IN PYRIDOXINE DEFICIENCY

With Notes on Similarities to Human Arteriosclerosis

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AND
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IN THE year 1948 we first reported the occurrence of arteriosclerotic lesions in rhesus monkeys subjected to pyridoxine deficiency.[1] The experimental method and some detail of the early findings were published in 1949.[2] Since that time the work has been extended to the study of 18 animals. This report is concerned with an analysis of the genesis of the lesions so produced and with a delineation of basic similarities of the experimental disease and human arteriosclerosis.

A prominent feature of the experimental process has been the accumulation in the intima and at times in the media of a mucoid intercellular substance exhibiting the metachromatic staining property characteristic of mucopolysaccharides. In our studies we have used toluidine blue to demonstrate the mucinous ground substance.

The vascular lesions of the pyridoxine-deficient monkeys are widespread. Arteries of all sizes are involved. While the basic features and general pattern of the experimental arteriosclerotic lesion are similar, there is naturally some variation in the precise appearance in vessels of different sites and sizes.

The vascular lesions have regularly occurred in the abdominal aorta and the iliac arteries (fig. 1), but significant lesions have not been seen in the thoracic aorta or the carotid arteries.

In the normal aorta one can demonstrate a small amount of metachromatic ground substance in the intima and surrounding the elastic tissue fibers of the media. In pyridoxine deficiency there is a manifest increase in the amount of this mucoid material in the intima (fig. 2*A*). Concomitant with the accumulation of the mucinous ground substance there is a proliferation of the cellular elements of the intima, and delicate fibers of collagen and imperfect elastic tissue are readily demonstrated (figs. 1 and 3). Electron micrographs indicate that the mucinous material is also rich in extremely delicate fibrils that are finer than could be revealed by light microscopy. It seems probable that the mucoid material is a mother substance which normally acts as an effective cement and from which collagen and elastic tissue fibers are maintained and formed. In pyridoxine

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1. Rinehart, J. F., and Greenberg, L. D.: Federation Proc. **7**:278, 1948.
2. Rinehart, J. F., and Greenberg, L. D.: Am. J. Path. **25**:481, 1949.

deficiency, perhaps through an interference with protein metabolism, this normal mechanism is disturbed and an excess of the ground substance accumulates. In addition to the new formation of collagen or elastic fibers, degeneration of pre-existing elastic tissue fibers is often demonstrable (fig. 4). While the reaction is dominantly intimal, there is often a swelling of metachromatic material in the media (fig. 4). In the older lesions lipid substances may accumulate in the sclerotic intima (fig. 5). This is usually most prominent in the deeper layers of the sclerotic plaques and appears to be a secondary rather than a primary feature of the pathologic process. In one instance only was calcification prominent (fig. 6).

The sclerotic changes in smaller arteries appear to be fundamentally similar. Here again metachromatic mucinous material accumulates in the intima and collagenous fibers develop in the abnormal matrix. The lesions have been prominent in renal arteries of all sizes with the exception of the arterioles. Note-

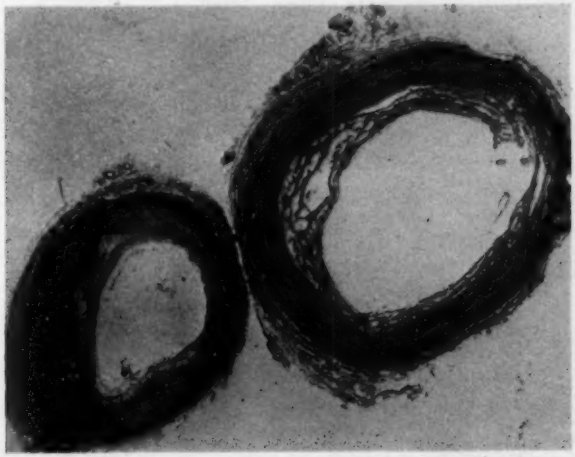

Fig. 1.—Lower abdominal aorta and iliac artery showing intimal sclerosis and elastosis; Weigert–Van Gieson stain; × 12. It is of interest that the iliac artery shows a plaque of dense elastosis deep to another plaque of looser texture superimposed, probably representing recurrent injury due to deficiency. This animal (M-1) was subjected to three episodes of pyridoxine deficiency of 12, 14 and 4 months' duration.

worthy occlusive sclerotic lesions are commonly found. The relationship of the accumulated metachromatic ground substance to the intimal sclerosis is well shown in figure 2*B* and *C*. Stained with toluidine blue, the thickened intima shows the rosy staining reaction of metachromasia (fig. 2*B*). The collagenous fibers in this substance are demonstrated by the Weigert–Van Gieson stain (fig. 2*C*). Similar changes are found in other visceral arteries, although they are somewhat less prominent. Occasionally, small arteries show accumulation of considerable amounts of mucinous material in the media separating the muscle cells, which undergo hypertrophy and proliferation (fig. 7). Lesions of this type bear considerable resemblance to the "glassy medial hypertrophy" described by Gross [3] in

3. Gross, L.; Kugel, M. A., and Epstein, E. Z.: Am. J. Path. **11**:253, 1935.

the small blood vessels of the heart in rheumatic fever and other febrile states. The arteries in the testicular tunic of the deficient animals have ordinarily shown

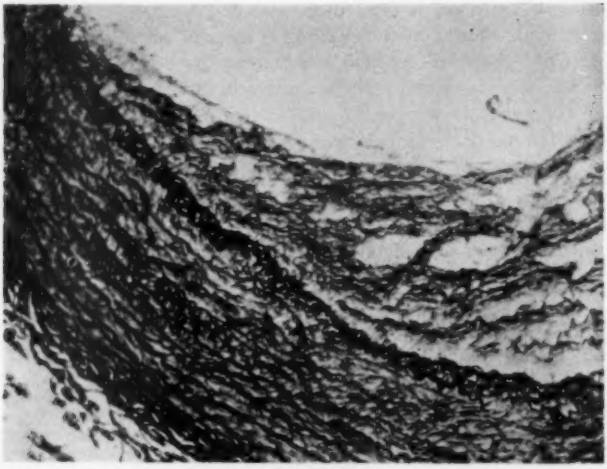

Fig. 3.—Abdominal aorta showing newly formed elastic tissue fibers in the thickened intima; Weigert–Van Gieson stain; × 80. M-14; pyridoxine deficiency six months.

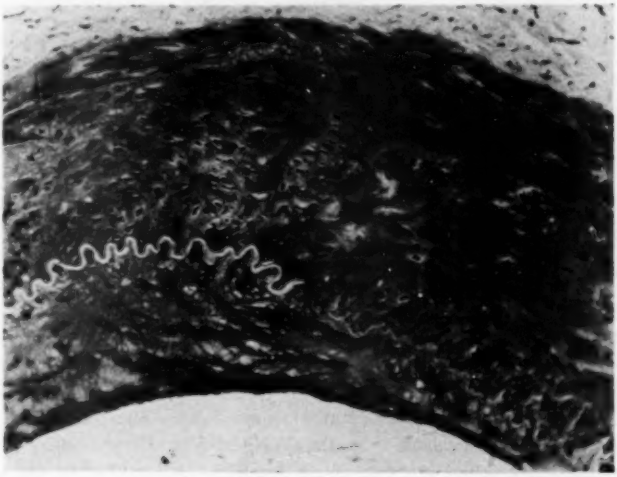

Fig. 4.—Cellular proliferation of the thickened intima of an iliac artery; thionine stain; × 160. The dark grayish matrix in the intima and in the media is a mucoid material which exhibits metachromatic staining properties. Degeneration of a part of the internal elastic membrane is evident. M-11; pyridoxine deficiency 11 months.

prominent occlusive sclerotic changes with marked metachromasia, both in the thickened intima and in the media (fig. 2 *F* and *G*). We have previously noted

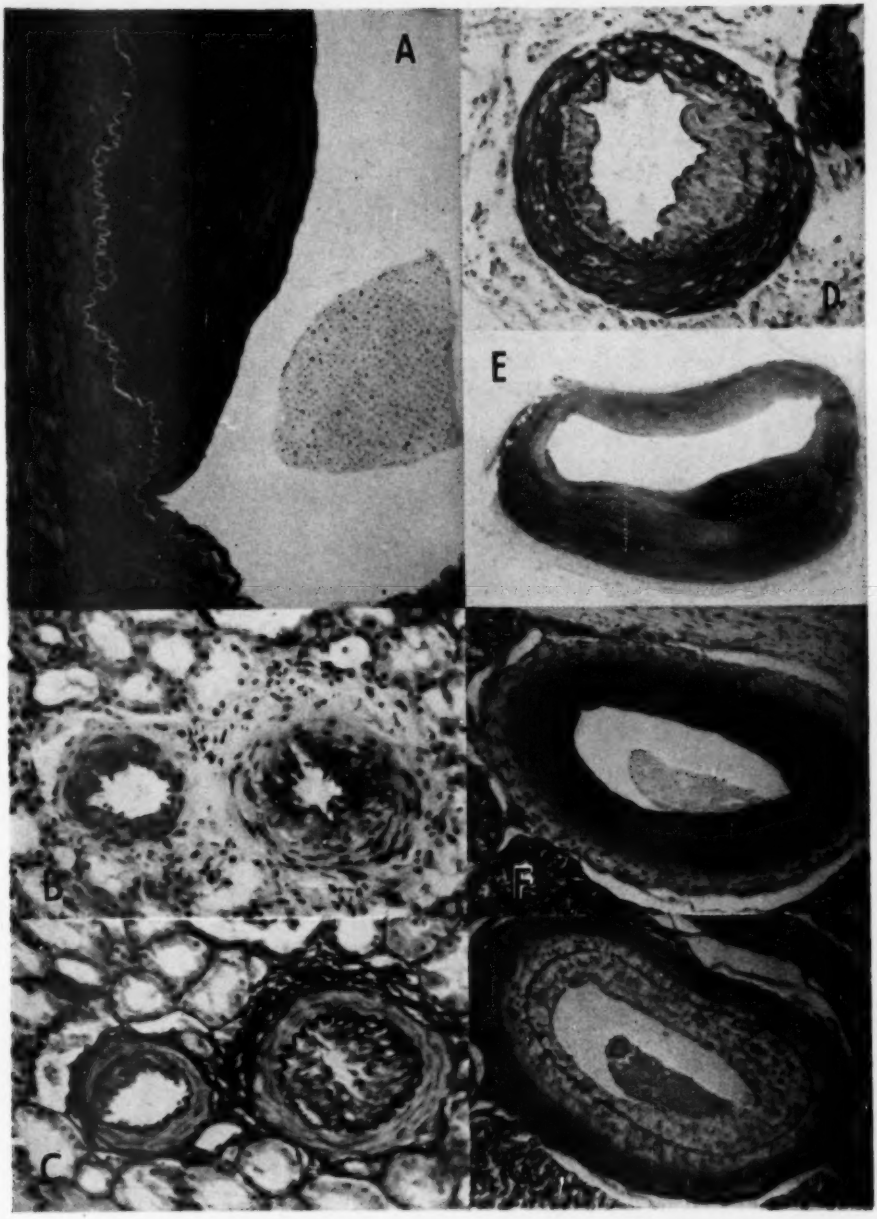

Fig. 2.—*A*, intimal plaque in the iliac artery which shows a mucinous matrix exhibiting dark metachromatic staining with toluidine blue. M-12; pyridoxine deficiency seven months and 12 months.

B, two small renal arteries; toluidine blue; × 80. The intima is markedly thickened by the accumulated mucopolysaccharide, which shows the property of metachromasia. M-1.

C, same vessels as shown in *B* stained by Weigert–Van Gieson method; × 80. The striking collagenous intimal thickening is evident. It will be seen that this corresponds with the zones of metachromasia shown in *B*.

D, small artery from the mesentery of the colon in a woman aged 42; toluidine blue; × 80. The accumulation of a metachromatic mucinous material in the intima is evident.

E, coronary artery from a man aged 31, with advanced coronary sclerosis; toluidine blue; × 12. Metachromatic mucoid substance is seen in the thickened intima and, to a lesser extent, in the media.

F, artery in the testicular tunic; toluidine blue; × 80. It will be seen that the intima and the media both exhibit marked metachromasia. M-1.

G, same vessel as shown in F stained by the Weigert–Van Gieson method; × 80. The marked occlusive intimal proliferation is evident. Delicate collagen fibers are present in the thickened intima.

and illustrated [2] the plaquelike distribution of lesions encountered in the coronary arteries.

There is no doubt that the sclerotic arterial lesions are related to the pyridoxine deficiency. Lesions of this character, which regularly develop in pyridoxine deficiency, have not been found in other deficient states or in control animals maintained on adequate supplements of pyridoxine.

To what extent is this experimental arteriosclerosis related to the spontaneous disease in man? At present it can be related only by analogy and inference. The morphologic analogies appear substantial. During the past two years we have studied the morphologic sequences in the development of human arteriosclerosis,

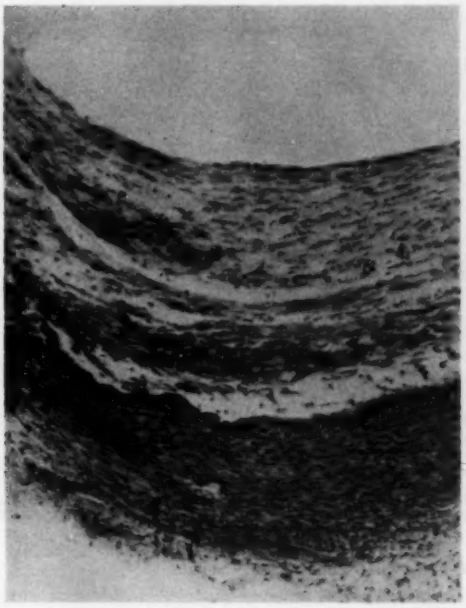

Fig. 5.—Abdominal aorta showing marked hyperplastic intimal thickening; sudan IV and hematoxylin; × 80. The dark cells deep in the intima are heavily laden with fat droplets. M-4; pyridoxine deficiency 19 months.

paying particular attention to the changes seen in the coronary arteries.[4] It is our belief that the disease in man is one which is primarily degenerative and proliferative in character and that in the majority of cases the appearance of lipids and cholesterol occurs later and probably represents a secondary phenomenon. Earlier studies of arteriosclerosis, as well as the observations in our laboratory, substantiate this point of view. It is of interest that the early histologic studies of Virchow [5] support the concept. He found the earliest change in arteriosclerosis

4. Moon, H., and Rinehart, J. F.: Unpublished data.

5. Virchow, R.: Gesammelte Abhandlungen zur wissenschaftlichen Medicin, Frankfurt, Meidinger Sohn u. Comp., 1856.

to occur in the intima and to consist of a gelatinous swelling of this layer. He noted that the material present resembled mucus both chemically and morphologically and observed the presence of delicate elastic fibers in this "structureless diaphanous intercellular substance." He considered that the gelatinous swellings were contributed to by imbibition of fluids from the blood stream. Concomitant with the alteration of the ground substance he noted that the connective tissue cells enlarged and multiplied. Aschoff [6] accepted this concept and placed particular emphasis on the thesis of lipid imbibition at the sites of degeneration. Schultz [7] considered a mucoid alteration of the intima as the basic lesion of arteriosclerosis and presented substantial evidence for this view. He believed the mucoid substance had a special affinity for lipids. Faber [8] has presented a similar view. This is an undoubtedly attractive thesis. Our own observations also indicate

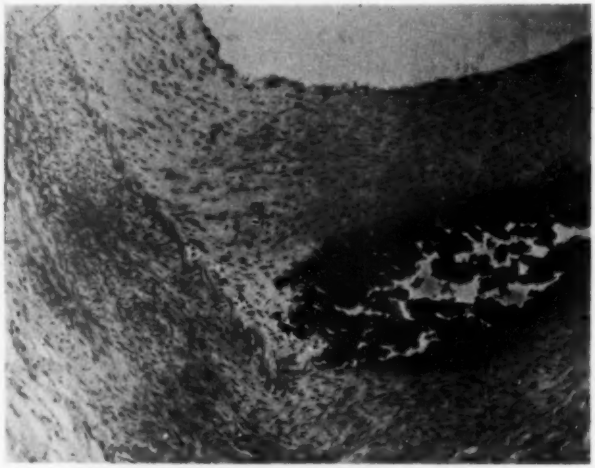

Fig. 6.—A mass of calcium deep in the sclerotic intima of the abdominal aorta; hematoxylin and eosin; × 80. M-4; pyridoxine deficiency 19 months.

that the early lesions of arteriosclerosis are characterized by accumulation of a mucoid substance in the intima (fig. 2 *D* and *E*) associated with cellular proliferation and deposition of collagen and elastic tissue. In the coronary arteries we find little evidence that deposition of lipid substances is a primary factor, even though it may be prominent in the later phases. In some instances only one segment of uniformly thickened intima may contain lipids while an adjoining segment shows metachromasia devoid of lipid. The lipids are found usually in the deeper layers of the thickened intima and their presence is often found in close association with degenerative changes in cells and intercellular substance. This suggests that the

6. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, p. 131.

7. Schultz, A.: Virchows Arch. f. path. Anat. **239**:415, 1922.

8. Faber, M.: Human Aorta: Sulfate-Containing Polyuronides and Deposition of Cholesterol, Arch. Path. **48**:342 (Oct.) 1949.

accumulation of fat represents a secondary and probably degenerative phenomenon. In the human disease the metachromasia may be somewhat less striking and the deposition of collagen more prominent than in the experimental disease. This may be related to a more gradual evolution of the human lesions. In the aorta the process appears to be somewhat different as compared with that in the coronary arteries. In the human aorta the lipid accumulation in the thickened intima is commonly seen early. It is found in association with the mucinous swelling characterized by the metachromatic staining property. The phenomenon of a lipid imbibition may be more prominent in the aorta than it is in smaller arteries. It is noteworthy, however, that the lipid is irregularly distributed and may be seen not only in the intima but also in the media.

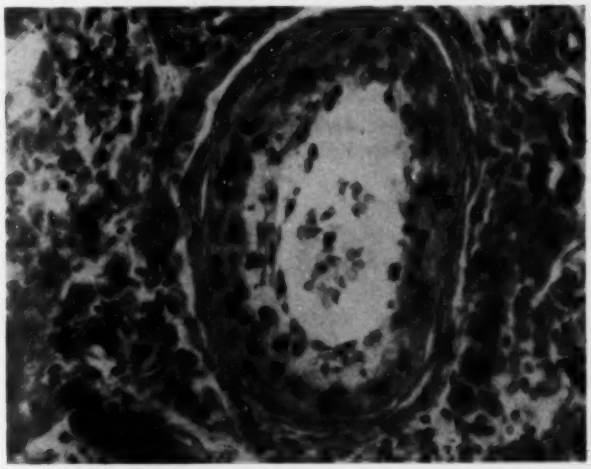

Fig. 7.—Small renal artery showing separation and proliferation of cells in the intima and media; Masson's stain; × 320. M-1.

COMMENT

There is no doubt that the widespread arterial lesions of pyridoxine deficiency in the rhesus monkey bear a close resemblance to those of human arteriosclerosis. The fundamental pathologic process appears to be similar. The accumulation of a mucoid metachromatic material in the intima and the associated proliferation of cells and deposition of collagen and elastic tissue fibers in the mucinous matrix appear to constitute the basic pathologic processes in each.

While the histological analogy is substantial and it seems probable that comparable pyridoxine deficiency in man would cause lesions of the type seen in the monkey, it does not follow that pyridoxine deficiency is necessarily concerned in the genesis of the human disease. Further study will be essential to establish the possible role of this deficiency in arteriosclerosis. In the monkey pyridoxine deficiency develops in a subtle manner and does not have distinctive external manifestations. The human requirement for pyridoxine is not yet established.

The accumulation of lipids appears ordinarily to be a later development in the evolution of arteriosclerosis. The exact sequences occurring in the evolution of arteriosclerosis and the derivation of the fatty substances deserve more extended study. The postulate that mucopolysaccharides have a special affinity for lipids is attractive and should be investigated further. The possibility that the lipid may be derived from degeneration of the mucopolysaccharide should also be considered.

SUMMARY AND CONCLUSIONS

Arteriosclerotic lesions develop regularly in the rhesus monkey subjected to prolonged pyridoxine deficiency. The initial lesion is characterized by the accumulation of a mucinous substance in the intima and, to a less extent, in the media of the arteries involved. This material exhibits the metachromatic staining property characteristic of mucopolysaccharides. Associated with the accumulation of this substance, cellular proliferation occurs and collagenous and elastic tissue fibers are formed. Studies of human arteriosclerosis indicate that basically similar sequences are seen in the evolution of the human disease. The role of lipids in the experimental and the human disease is briefly discussed. The morphologic features of the experimental vascular lesions and those occurring in man are similar. The possible role of pyridoxine deficiency in the etiology of human arteriosclerosis remains to be determined.

EFFECT OF STRONTIUM CHLORIDE FEEDING ON THE RAT MOLARS AND THEIR SUPPORTING TISSUES

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THE EFFECTS of strontium on dentin, enamel and bone in the incisor of the rat have been studied previously: Strontium was found to cause a calcio-traumatic response in the dentin of the rat incisor.[1] Large doses of strontium produced hypoplastic changes in the enamel.[2] Strontium, when made to replace calcium in the diet, led to rickets-like changes in the long bones.[3] The present investigation deals with the effects of strontium on the cementum, the periodontal membrane and the alveolar bone of the molars of the rat.

TABLE 1.—*Age and Weight of Control and Experimental Animals*

Group	Animals	Age at Start, Days	Experiment	Weight at Start, Gm.	Weight at Autopsy, Gm.	Age at Autopsy, Days
1	6	21	Control	27-39	126-184	66-74
2	5	21	1% $SrCl_2$	25-35	84-97	66
3	6	21	2% $SrCl_2$	25-30	55-122	71-74

MATERIALS AND METHODS

The present study is based on the histological investigation of the upper and lower molar regions of 17 albino rats (Wistar Institute).

Group 1: Six rats, after weaning, were fed on basal diet of dog chow [4] and water and were killed at varying intervals from 66 to 74 days of age (table 1).

Group 2: Five animals were fed the same basal diet after weaning and were given drinking water to which 1 per cent strontium chloride had been added. They were killed at 66 days of age (table 1).

Group 3: Six animals, after weaning, were fed the basal diet and were given drinking water to which 2 per cent strontium chloride had been added. The animals were killed at intervals from 71 to 74 days of age (table 1).

From the Department of Oral Medicine and Surgery, Meharry Medical College, Nashville, Tenn., and the Departments of Histology and Oral Pathology, University of Illinois College of Dentistry, Chicago.

1. (*a*) Weinmann, J. P.: J. Dent. Research **21**:497, 1942. (*b*) Irving, J. T., and Weinmann, J. P.: Ibid. **27**:669, 1948.

2. (*a*) Weinmann, J. P.: J. Am. Dent. A. **30**:874, 1943. (*b*) Irving, J. T., and Weinmann, J. P.: To be published.

3. Shipley, P. G., and others: Bull. Johns Hopkins Hosp. **33**:216, 1922.

4. The chow used was that produced by the Ralston Purina Company, St. Louis.

After an animal was killed, the jaws were fixed in formaldehyde solution U. S. P. diluted 1:10 and then decalcified in 5 per cent nitric acid. The molar regions of the upper and lower jaws were dissected, embedded in celloidin (pyroxylin), serially sectioned in a mesiodistal direction and stained with hematoxylin-eosin.

FINDINGS

The following description is based mainly on the study of the first and the second upper and lower molars and their supporting structures.

The strontium chloride added to the drinking water caused disturbance in the calcification of dentin, cementum and alveolar bone. The changes following the drinking of water containing 1 per cent and 2 per cent strontium chloride, respectively, were similar in character but were more pronounced in the group receiving the higher concentration. The changes also varied in the different molars of the same animal, the second molars being more affected than the first.

CONTROL ANIMALS (GROUP 1).—A description of the control molars and their supporting tissues is presented so that the strontium-affected molars of the experimental animals may be compared with them.

Dentin.—The calcified dentin is covered on the pulpal surface by a layer of uncalcified predentin, which is thicker on the roof of the pulp chamber than on the floor (table 2). The most peripheral layer of dentin forming the root, that is, the subcemental dentin, stains light purple, while the main portion stains dark purple. On the basis of previous studies,[1b] this difference in the staining reaction can be interpreted as an indication that the subcemental dentin is richer in fibrils than the rest of the dentin and therefore contains less calcifiable cementing substance. It should be stressed that the subcemental dentin is limited to the root only.

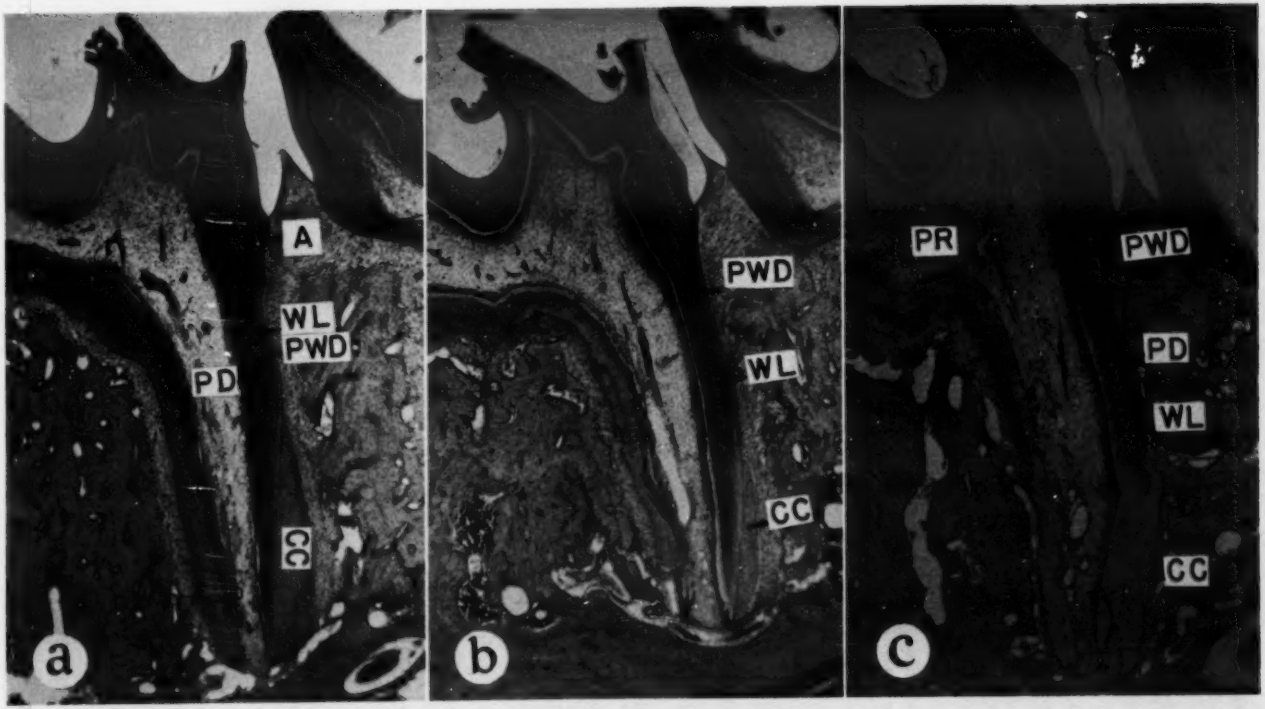
The dentin formed at the time of weaning shows a characteristic response to the change of the nutrition in the form of a "weaning band." The weaning band consists of three stripes: most peripherally the darkly stained calciotraumatic line, followed by a layer of uncalcified dentin, and toward the pulp a wider, darkly staining stripe of hypercalcified dentin, which fades gradually into the normal staining of the central dentin.

The weaning line ends at the dentinal surface at the border between the middle and apical third of the root (figs. 1*A* and 2*A*, showing that at the time of weaning only two thirds of the root of the first molars had been formed.

Cementum.—The cervical and middle third of the root is covered by a thin layer of acellular cementum. The apical third of the root is covered by a layer of cellular cementum which increases in thickness toward the apex.[5] Between the dentin and the cellular cementum, some islands of spindle-shaped connective tissue cells can be seen. The most superficial layer of the cementum (6 microns thick) consists of cementoid tissue. The latter is uncalcified and stains with eosin only. Resorption of cementum is rare. When found, it is confined to the acellular cementum and is on only those surfaces of the roots which face distally.

Periodontal Membrane.—The periodontal membrane is of more or less even width all around the tooth. The principal fibers run from points on the alveolar

5. Hoffman, M. M., and Schour, I.: Am. J. Orthodontics **26**:854, 1940.



EXPLANATION OF FIGURE 1

Photomicrographs of decalcified mesiodistal sections of the distal roots of lower first molars. The space originally occupied by the enamel was lost during decalcification. All illustrations were prepared from sections stained with hematoxylin and eosin. × 40.

(*a*) Normal control rat (no. 8), 71 days old. Note the thin layer of subcemental dentin at *A*, the physiological weaning line (*WL*), the preweaning dentin (*PWD*), the postweaning dentin (*PD*) and the calcified cellular cementum (*CC*).

(*b*) Rat 15, which received 1 per cent strontium chloride from weaning to 66 days of age. Note weaning line (*WL*), preweaning dentin (*PWD*), the hypocalcified stripe of dentin and the thin mantle of calcified cellular cementum (*CC*), which is peripherally lined by a layer of cementoid tissue.

(*c*) Rat 3, which received 2 per cent strontium chloride from weaning to 74 days of age. Note weaning line (*WL*), preweaning dentin (*PWD*), striated postweaning dentin (*PD*), and the uncalcified predentin (*PR*) and cellular cementum (*CC*). Compare the thickness of the dentinal wall at the cementoenamel junction and that of the predentin (*PR*) at the root bifurcation with that of the normal control (*a*).

bone to more apical points on the root. The fibroblasts between them are arranged in such a way that their long axes follow the general direction of the fibers (figs. 1 *A* and 2 *A*).

Alveolar Bone.—The interdental and interradicular septums show a consistent picture. Howship's lacunas and osteoclasts are seen on the surface facing mesially. The surfaces facing distally show a thin layer of osteoid tissue covered by osteoblasts.

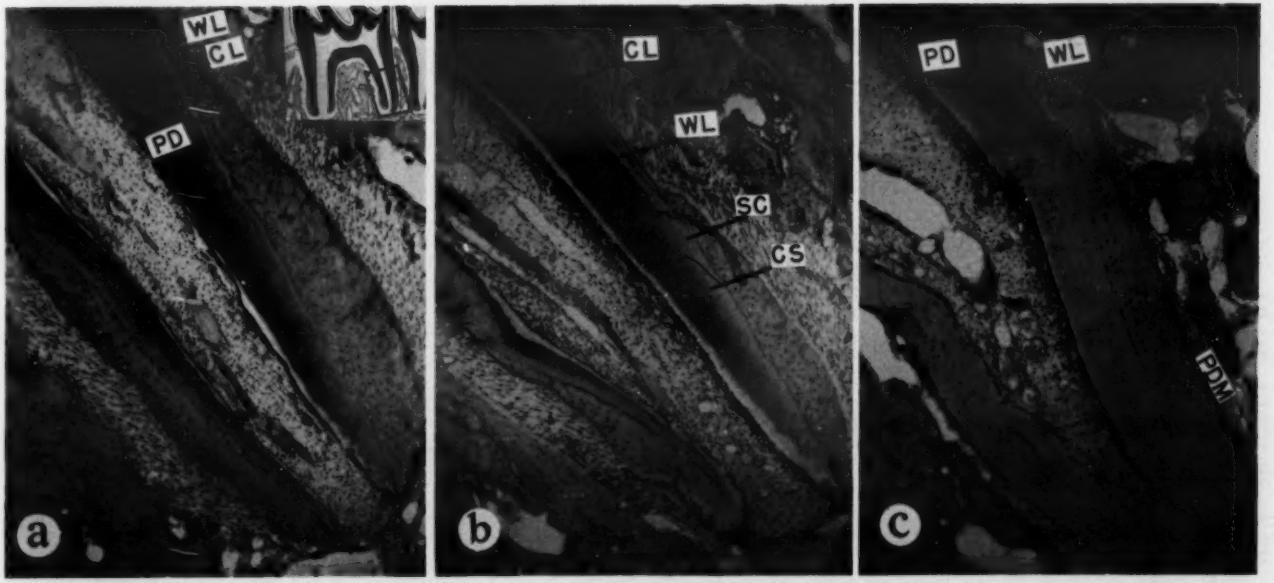
Rats Receiving 1 Per Cent Strontium Chloride (Group 2).—*Dentin.*—The over-all length of the roots was found to be the same as in group 1 (table 2). The width of the dentinal wall (measured at the cementoenamel junction) was reduced by about 10 per cent as compared with the controls. The average width of the predentin was increased to more than twice that of group 1 (table 2).

Table 2.—*Average Measurements of the Lengths of Distal Roots and the Widths of Dentin, Predentin and Cementoid Layer in the Maxillary and Mandibular First and Second Molars of the Control and Experimental Animals*

Measurements	Groups	Maxillary		Mandibular	
		1st Molar	2d Molar	1st Molar	2d Molar
Length of distal root, mm.	1	1.8	1.4	2.4	2.0
	2	1.9	1.5	2.3	1.9
	3	1.7	1.4	2.4	1.8
Width of predentin at roof of pulp chamber, microns	1	13.0	9.0	14.0	18.0
	2	29.0	21.0	35.0	26.0
	3	37.0	58.0	43.0	65.0
Width of predentin at floor of pulp chamber, microns	1	7.0	7.0	8.0	6.0
	2	15.0	17.0	18.0	19.0
	3	49.0	51.0	76.0	79.0
Width of dentin at cementoenamel junction of distal root, microns	1	244.0	219.0	348.0	296.0
	2	229.0	210.0	306.0	277.0
	3	201.0	181.0	278.0	251.0
Width of cementoid layer at apical third of distal root, microns	1	.....	.....	6.0	6.0
	2	.....	.....	17.0	10.0
	3	.....	.....	90.0	76.0

The weaning band which in groups 2 and 3 separates the preexperimental from the strontium-affected dentin was wider than in the normal animals and gradually increased in thickness from the crown to the root. Also the subcemental layer of dentin in the part of the root which formed during the experiment was wider than normal. The boundary between the subcemental and the adjacent layer of dentin was irregular. The latter showed disturbance in calcification (interglobular dentin) (fig. 2 *B*).

Cementum.—The acellular cementum covered a larger portion of the root but was otherwise unchanged (fig. 1 *B*). The cellular cementum covered a shorter section of the root and was reduced in thickness as compared with the controls. The point at which the weaning line reaches the cemental surface of the dentin can conveniently be used as a landmark to distinguish the part of the root formed before weaning from the part which forms after it (fig. 2 *A* and *B*). In the controls the cellular cementum covered a small part of the root which was formed before weaning. In the experimental animals, only the root formed after weaning was covered by cellular cementum. The islands of connective tissue cells between dentin and secondary cementum appeared somewhat more numerous and larger in the experimental animals. The cementoid tissue was about three times the thickness found in the control animals (table 2).



EXPLANATION OF FIGURE 2

Photomicrographs of mesiodistal sections of the distal roots of lower first molars. The area is indicated in the insert in part (*a*). ×80.

(*a*) Normal control rat (no. 8), 71 days old. Note the weaning line (*WL*), peripherally lined by the calciotraumatic line (*CL*), and the postweaning dentin (*PD*).

(*b*) Rat 15, which received 1 per cent strontium chloride from weaning to 66 days of age. Note the accentuated weaning line (*WL*), the calciotraumatic line (*CL*), the wide subcemental layer of dentin (*SC*), the irregular calcospherites (*CS*) and the mantle of cellular cementum peripherally lined by a wide layer of cementoid tissue.

(*c*) Rat 3, which received 2 per cent strontium chloride from weaning to 74 days of age. Note the accentuated weaning line (*WL*), the striated appearance of the postweaning dentin (*PD*) and the uncalcified predentin and cementoid tissue of the apical third of the root. *PDM* indicates periodontal membrane; compare it with that in figures *2 a* and *2 b*.

Incidence and severity of resorption of the roots were greater than in the controls. As in the normal rats, resorption was restricted to the gingival half of the roots and was most frequently found on the distal surface and in the bifurcation. In many instances the resorption areas penetrated to a slight degree into the dentin. Resorption of the cellular cementum was not observed.

Periodontal Membrane and Alveolar Bone.—The pattern of bone apposition and resorption, the width of the periodontal membrane and the structural arrangement of the principal fibers were as in the control animals.

Rats Receiving 2 Per Cent Strontium Chloride (Group 3).—All changes observed following the administration of 1 per cent strontium chloride in the drinking water were greatly exaggerated after the administration of 2 per cent strontium.

Dentin.—The over-all length of the roots was the same as seen in the controls and in the rats receiving 1 per cent strontium chloride. The dentinal wall, measured at the cementoenamel junction, was reduced by 20 per cent as compared with the controls. The average width of the predentin at the roof of the pulp chamber was found to be increased to about three times and that at the floor to about eight times the normal (table 2). The predentin increased in width from the crown to the apex of the root. The dentin formed before weaning, with the exception of subcemental dentin, was stained evenly purple. The subcemental dentin was stained lighter.

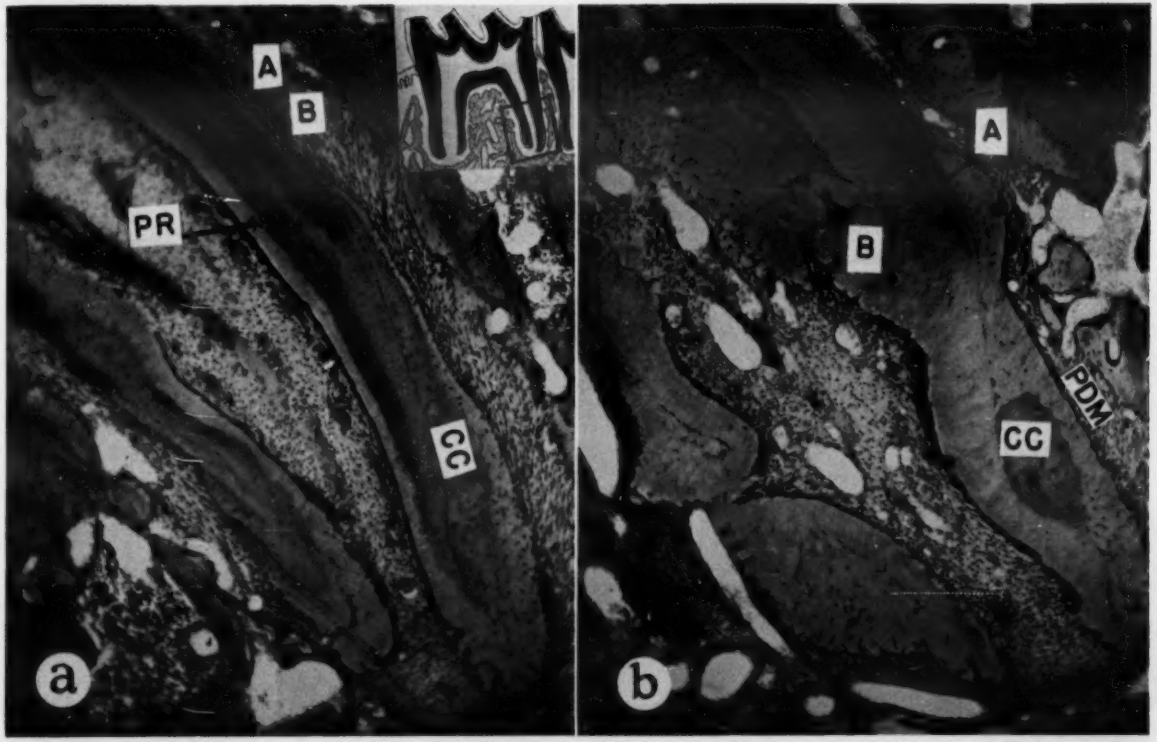
The weaning band was more accentuated than in the animals receiving 1 per cent strontium chloride. Toward the pulp the traumatic response was followed by a layer of normally stained dentin, but one or even two recurrences of a traumatic response were found. This alteration of normal and traumatized dentin gave the dentin a striated appearance (fig. 3 *A*).

In extreme cases the dentin of that portion of the roots which formed after the beginning of the experiment remained uncalcified (figs. 1 *C* and 2 *C*). In some animals the innermost layers of the dentin showed the same picture as was seen in animals given 1 per cent strontium chloride (fig. 3 *A*). In others, only islands of calcified tissues which consisted of calcified dentin or cementum could be observed (fig. 3 *B*).

Cementum.—The acellular cementum covered a greater portion of the root than it did in the control animals, but its structure was unchanged. The cellular layer was entirely uncalcified in extreme cases; in other cases the degree of calcification resembled that found in rats given 1 per cent strontium chloride (fig. 3 *A*). In intermediate cases, only the central part of the cellular cementum was calcified (fig. 3 *B*).

The number and the extent of the resorption areas were considerably increased beyond those found in the group which was given 1 per cent strontium chloride. The resorption areas were confined only to that part of the roots which was covered by acellular cementum (fig. 4).

Periodontal Membrane and Alveolar Bone.—On their gingival surfaces, the interdental and the interradicular septums were covered by a variably thick layer of osteoid tissue. The amount of osteoid tissue increased from the region of the



EXPLANATION OF FIGURE 3

Photomicrographs of mesiodistal sections of the distal roots of lower first molars. The area is indicated in the insert of (*a*). × 110.

(*a*) Rat 1, which received 2 per cent strontium chloride from weaning until 74 days old. The pattern of calcification seen here is similar to that seen in figure *2 B*. Note the weaning line at *A*, the hypocalcified stripe at *B*, predentin (*PR*), calcified cementum (*CC*) and the light layer of cementoid tissue at the periphery.

(*b*) Rat 2, which received 2 per cent strontium chloride from weaning until 74 days old. Note the weaning line at *A*, the irregular formation of dentin at the midroot area *B*, and a core of cellular cementum (*CC*) which appears calcified at the apical third of the root. Also note the irregularity of the periodontal membrane space (*PDM*).

first molar to that of the third. In the latter, it formed as much as the gingival one third or half of the bony septums. The surfaces of the bony septums facing distally showed a consistent picture of bone apposition. On the surfaces facing mesially, either bone apposition or inactivity was seen. Bone resorption was not observed. The width of the periodontal space was reduced and was uneven in almost all instances (figs. 2 *C* and 3 *B*). The reduction of width was more marked in the regions of the second and third molars than in those of the first molars. Frequently the reduction was extreme, leading to complete obliteration of the periodontal

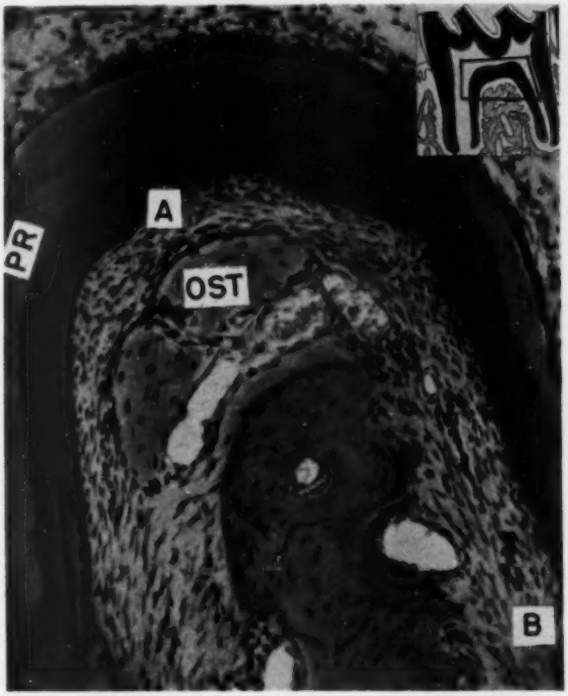


Fig. 4.—Photomicrograph of a mesiodistal section of the bifurcation of a lower first molar. The area is indicated in the insert. × 180. The rat (no. 10) received 2 per cent strontium chloride from weaning to 71 days of age. Note the resorption of primary cementum extending from *A* to *B*, the excessive width of the predentin, (*PR*) and the osteoid tissue (*OST*) on the crest of the alveolar septum.

membrane. In such cases osteoid and cementoid tissues were in contact with one another.

The periodontal membrane was disorganized. In many places it had lost the characteristic arrangement of its principal fibers and consisted of loose connective tissue. In others the fibers, instead of running at an angle to the root surface, were arranged parallel to it. The number of fibroblasts per unit area was increased.

COMMENT

In evaluating the changes produced by administering strontium chloride, we have attempted to answer the following questions: First, which aspects of the development of the dental tissues are affected, and, second, how do the changes produced by strontium compare with the changes found in rachitic rats?

Growth of Teeth.—The increase in root length proceeded at a normal rate (table 2). From this observation it may be concluded that the proliferation of Hertwig's epithelial sheath and of the pulpal tissue continued in a normal manner. The morphogenetic function of Hertwig's sheath in determining the shape of the root of the tooth and the organizing function in causing the connective tissue cells to differentiate into odontoblasts was undisturbed. Whereas dentin formation progressed in length at a normal rate, the increase of the thickness of the dentin wall was reduced, indicating a reduced rate of odontoblastic activity.

Calcification.—The calcification of dentin and cementum was disturbed. The disturbance was more evident after the administration of 2 per cent strontium chloride than after 1 per cent strontium chloride (table 2). In the latter case the calcification improved after the initial disturbance, indicating a recovery of the damaged odontoblasts. Ameloblasts showed a similar recovery after being injured by strontium chloride.[2a]

With 2 per cent strontium chloride, the dentin formed in the gingival two thirds of the root was striated, indicating repeated calciotraumatic responses.[1b] It seems that the odontoblasts which had started to function before the experiment were injured, recovered and again suffered injury after a short period of recovery. This peculiar phasic susceptibility of the odontoblasts suggests brief periods of adaptation which are overcome by the continuous action of the injurious element.

As stated above, the dentin of the apical third of the root showed in extreme cases complete lack of calcification. This observation suggests that odontoblasts are more susceptible to strontium injury while in the process of differentiating than in stages when their differentiation is completed.

Whereas 2 per cent strontium chloride led to an accumulation of large amounts of osteoid tissue in the alveolar bone, 1 per cent strontium chloride did not affect the calcification of bone but did produce slight disturbances in the calcification of dentin. It appears, therefore, that the calcification of dentin is more easily disturbed than the calcification of bone.

Periodontal Membrane.—Rats receiving 2 per cent strontium chloride showed narrowing or obliteration of the periodontal spaces and disorganization of the periodontal fibers. These changes were more marked on the distal sides of the root.

It would seem that the narrowing of the periodontal spaces is caused by an interference with the physiological distal drift of the rat molars.[6] Normally, apposition of bone is found on the mesial, resorption on the distal, wall of the alveoli. The bone formed during the experimental period remained uncalcified. It has been shown repeatedly that uncalcified bone is resistant to resorption.[7] Since in animals

6. Sicher, H., and Weinmann, J. P.: Am. J. Orthodontics **30**:109, 1944.

7. Gottlieb, B.: Ztschr. f. Stomatol. **18**:59, 1920. Kronfeld, R.: Ibid. **25**:1099, 1927. Orban, B., and Weinmann, J. P.: Virchows Arch. f. path. Anat. **267**:446, 1928. Weinmann, J. P., and Schour, I.: Am. J. Path. **21**:833, 1945.

fed 2 per cent strontium chloride bone apposition on the mesial wall progresses but resorption on the distal wall is prevented, the result is an encroachment on or obliteration of the periodontal space.

Sensitivity of Cells to Strontium.—Administration of strontium affected dentin, cementum and bone. One per cent strontium chloride affected only the dentin and the cementum; 2 per cent strontium chloride also affected the calcification of bone. This indicates that the odontoblasts and cementoblasts are more sensitive to strontium than the osteoblasts. The greater sensitivity of the odontoblasts to changes in the metabolic environment may provide a useful tool in experimental histophysiology.

That the ameloblasts of the rat incisor are sensitive to high doses of strontium has been shown previously.[2a] This finding is not contradicted by the fact that in the present investigation the enamel of the molars did not show any changes, since at the time at which the experiment was started the enamel of all the molars had already been completed.

Comparison with Rickets.—The morphological changes in the molars and their supporting structures due to strontium administration and those observed in experimental rickets appear comparable in many respects. Both in strontium feeding and in experimental rickets the width of predentin and cementoid tissue is increased. In both cases the bone formed during the experimental period does not calcify and does not undergo resorption. There are, however, differences in the appearance of hypocalcified dentin in rickets and the hypocalcified (calciotraumatic) dentin seen after strontium feeding. In the former the dentin is globular, while in the latter it appears striated. Furthermore, it has been shown that strontium chloride consistently produced hypoplasia of the enamel,[2a] whereas in experimental rickets the formation of enamel is not affected.[8] Sobel and co-workers[9] showed that in rickets the bone matrix is "calcioreceptive" and that when slices of rachitic bone are incubated with artificial serum solutions, calcification occurs.[9] The bone matrix of the strontium-fed animals, on the other hand, does not calcify when incubated with artificial serum.[9] Although studies on the effect of strontium on calcium and phosphorus blood levels have not been performed, the experiments of Sobel and co-workers permit the conclusion that, in contradistinction to rickets, strontium feeding causes a qualitative change in the bony matrix. It is therefore suggested that the changes following strontium administration be designated as "strontium intoxication" instead of "strontium rickets."

SUMMARY AND CONCLUSIONS

Strontium chloride added to the drinking water of white rats in concentrations of 1 and 2 per cent produced changes in the molars and their supporting structures.

The changes were more marked in the group that received 2 per cent than in that which received 1 per cent strontium chloride.

The differentiation of odontoblasts was not affected, but the rate of their activity of dentin formation was reduced. Therefore, root length was normal, but the dentin was reduced in thickness.

8. Weinmann, J. P., and Schour, I.: Am. J. Path. **21**:821, 1945.

9. Sobel, A. E.; Goldfarb, A. R., and Kramer, B.: Proc. Soc. Exper. Biol. & Med. **31**:869, 1934.

Calcification of dentin, cementum and bone was disturbed. Dentin showed a calciotraumatic response and a wide predentin layer. Cementum showed a wide layer of cementoid tissue. Calcification of bone was disturbed only in the rats which received 2 per cent strontium chloride. Since in the group which received 1 per cent strontium chloride only calcification of dentin and cementum was disturbed, it may be concluded that the odontoblasts and cementoblasts are more sensitive than the osteoblasts.

Because the enamel formation had already been completed in the molars at the time the administration of strontium was started, the absence of change in the enamel does not indicate an immunity of ameloblasts to strontium.

A narrowing and obliteration of the periodontal spaces and a disorganization of the periodontal ligament fibers in rats given 2 per cent strontium chloride occurred because of the lack of resorption of the osteoid tissue on the distal wall of the sockets.

Morphological changes following strontium administration appeared similar but were not identical with those seen in experimental rickets.

UNILATERAL RENAL CORTICAL NECROSIS AND UNILATERAL BENIGN AND MALIGNANT NEPHROSCLEROSIS

Associated with Contralateral Renal Artery Occlusion: Report of a Case

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THE MECHANISMS of production of human hypertension have been the subject of considerable discussion and controversy since the classic experiments of Goldblatt [1] over a decade ago. Since he demonstrated sustained hypertension as a result of induced renal ischemia in animals, many instances have been cited of possible human counterparts of this experiment.[2] Numerous investigators,[3] in reexamining large series of their own cases, have reached the conclusion that no correlation exists between the luminal diameter of the renal artery and the presence of elevated blood pressure. Conversely, a number of papers have appeared describing bilateral occlusive changes in the renal arteries coincident with clinical hypertension.

In reviewing the latter cases, one is inevitably aware of the remote possibility that the interrelationship of the two factors (i. e., renal ischemia and hypertension) may have been entirely fortuitous. In order to reach a valid conclusion, it seems necessary to observe a condition wherein the blood supply to only one kidney would be impaired, with resultant hypertension. In such circumstances the contralateral kidney would be theoretically free to bear the brunt of the hypertensive state and manifest the classic microscopic change. If the ischemic kidney should fail to show similar vascular changes, it would then be reasonable to preclude hypertension of extrarenal origin in the observed case.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Goldblatt, H.: The Renal Origin of Hypertension, Springfield, Ill., Charles C Thomas, Publisher, 1948.

2. (*a*) Yuile, C.: Obstructive Lesions of the Main Renal Artery in Relation to Hypertension, Am. J. M. Sc. **207**:394-404, 1944. (*b*) Leiter, L.: Unusual Hypertensive Renal Disease, J. A. M. A. **111**:507-510 (Aug. 6) 1938. (*c*) Freeman, G., and Hartley, G.: Hypertension in a Patient with a Solitary Ischemic Kidney, ibid. **111**:1159-1162 (Sept. 24) 1938. (*d*) Stewart, C. F.: Arteriosclerosis of the Renal Artery Orifices with Severe Hypertension, ibid. **114**: 2099-2101 (May 25) 1940.

3. Lisa, J.; Eckstein, D., and Solomon, C.: Relationship Between Arteriosclerosis of the Renal Artery and Hypertension, Am. J. M. Sc. **205**:701-703, 1943. Oppenheimer, B.; Klemperer, P., and Moschkowitz, L.: Evidence for the Goldblatt Mechanism of Hypertension in Human Pathology, Tr. A. Am. Physicians **54**:69-81, 1939.

Cases which conform to the hypothetical conditions indicated above have been described.[4] The present case also fulfils these qualifications and, in addition, demonstrates a severe superimposed cortical necrosis limited to the arterially nonobstructed kidney.

REPORT OF CASE

A 52 year old white man was admitted to the hospital on Sept. 24, 1949, complaining of cough, fever, headaches and loss of weight.

Past Medical History.—The history prior to 1946 was noncontributory. In the summer of 1946, at which time the patient was asymptomatic, his blood pressure was 126/80. In the winter of 1947 the patient suffered great exhaustion and near unconsciousness attendant on an 8 mile struggle by foot through a snow storm (no chest pain). He suffered easy fatigability thereafter. In November 1948 a physical examination for life insurance disclosed a blood pressure of 130/90-86. At that time the urine showed a specific gravity of 1.025 and was otherwise normal except for one to two red blood cells and four hyaline casts per high power field. A survey type chest roentgenogram in February 1949 was interpreted as disclosing no abnormal condition.

History of Present Illness.—In April 1949 the patient noted onset of headaches, poor vision and loss of weight. In August 1949 he consulted an ophthalmologist, who suggested that he had "hypertension or diabetes." His family physician shortly thereafter discovered that the patient had hypertension. Nocturia and slight polyuria appeared four weeks before admission. A urinalysis at this time revealed no abnormality. One week prior to entering the hospital he had a sudden onset of a slightly productive cough, fever, with temperature ranging to 101 F. orally, and excessive perspiration. Ankle edema was noted for the first time the day before hospitalization, and the patient was digitalized. His temperature became normal a few days before admission.

Physical Examination (Sept. 24, 1949).—The patient was a well developed, fairly well nourished middle-aged man, who appeared chronically ill. Significant findings included pale optic disks and slight arteriovenous compression, numerous exudates and old and recent flame-shaped hemorrhages bilaterally in the fundi. The lungs were clear. The blood pressure was 170-180 systolic and 100-110 diastolic. There was no clinical cardiac enlargement. The heart sounds were of fair quality. No thrills or murmurs were noted. The rhythm was regular. There was no peripheral edema, cyanosis or venous distention. Otherwise the results of the examination were negative.

For purposes of clarity, the hospital course is divided arbitrarily into two periods (period A, September 24 to October 28, and period B, October 29 to November 8). The beginning of period B indicates the onset of the clinical symptoms of uremia.

Hospital Course, Period A.—In view of the history, the patient was digitalized for the first two days of hospitalization. However, he exhibited no evidence of congestive failure. The venous pressure and the circulation time were normal. He had a dry cough with almost no sputum. An admission electrocardiogram showed changes compatible with recent anteroseptal myocardial infarction. Admission chest roentgenograms showed bilateral upper pulmonary lobe infiltrations without cavitation. During the first month of hospitalization the patient was asymptomatic except for a nonproductive cough, malaise and occasional headache. There was no chest pain. Electrocardiograms showed serial changes compatible with the diagnosis of recent myocardial infarction. Further chest roentgenograms showed no change in the upper lobe lesions until October 23. There were no pulmonary physical signs.

The patient was afebrile from admission until October 23. From October 23 to October 26 the temperature varied between 100 and 101 F. orally. With the onset of fever there was an increase in cough and profuse diaphoresis; at this time, rales appeared in the lower left region of the chest, and a roentgenogram showed a new infiltrate there without change in the upper lobe infiltrates. The temperature returned to normal on October 26.

Blood pressures during period A were 155-180 systolic and 100-120 diastolic.

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4. Saphir, O., and Ballinger, J.: Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis, Arch. Int. Med. **66**:541-560 (Sept.) 1940. Yuile.[2a]

Laboratory Data, Period A.—The urine had a specific gravity of 1.008 to 1.013. One of the four specimens examined showed albumin (1 +) and numerous pus cells. The white blood cell count was 10,500, with a normal differential count. The hemoglobin content was 15.5 Gm. The red blood cell count was 4,700,000. Serologic tests for syphilis were negative. Blood urea nitrogen was 15 mg. per 100 cc. The phenolsulfonphthalein test demonstrated 10 to 15 per cent excretion in 15 minutes. Studies for tuberculosis (sputum smears, sputum cultures and gastric lavage cultures) revealed no acid-fast bacilli. Serum protein was 5.3 Gm. per 100 cc. The fasting blood sugar level was 89 mg. per 100 cc. An intravenous pyelogram on October 28 revealed poor filling of calices on the right and normal filling on the left side.

Hospital Course, Period B.—On October 29 the patient was noted to be restless and slightly tachypneic. The following day there was onset of weakness, diaphoresis and intermittent drowsiness. Laboratory tests on November 1 confirmed the impression of uremia and acidosis. On November 1 the temperature dropped from normal to 95 F. orally. Ascites and oliguria were noted. The blood pressure was 140/110. The following day the temperature rose to 104 F., accompanied with definite leukocytosis.[5] Simultaneously, there was recorded the onset of left anterior subcostal pain, peripheral edema and venous distention, basal pulmonary rales and anuria, the latter persisting for 38 hours. During this anuric phase the blood pressure was 160-180 systolic and 120 diastolic. After recovery from anuria, the blood pressure varied between 150 and 200 systolic and 110 and 130 diastolic. The fever lasted only 24 hours, disappearing during the period of anuria. The patient was digitalized, but, despite this, anasarca continued and increased until death.

The period of anuria was terminated when the patient voided 400 cc. of urine (specific gravity, 1.010) on November 3. Thereafter, he voided at least 500 cc. of urine per day.

In the last four days of life, bilateral crepitant basal rales were present, and a right pleural effusion became apparent. Beginning November 3, the patient complained intermittently of right upper quadrant abdominal pain accompanied with tenderness in the hepatic region. Prior to November 7 there were no cardiac thrills, murmurs or enlargement. Throughout the hospital course there was no chest pain. On November 7 a pericardial friction rub appeared. The patient died quietly on Nov. 8, 1949.

Laboratory Data, Period B.—The blood urea nitrogen on November 1 was 59 mg. per 100 cc. and rose rapidly till death. The carbon dioxide–combining power on November 1 was 31 volumes per cent. Daily urine specimens showed a specific gravity of 1.020 on November 1, and fixation between 1.010 and 1.012 thereafter. There was always albumin (3 or 4 +). Examinations of the urinary sediment disclosed numerous pus cells (not clumped) and granular casts, with only rare red blood cells. The white blood cell count on November 2 was 49,000 with 97 per cent polymorphonuclear granulocytes. Thereafter, the white blood cell count decreased to 26,000. Blood and urine cultures were negative. Cephalin flocculation (November 3) was 4 +. Serum bilirubin (November 3) was 2.1 mg. per 100 cc. Prothrombin time was 35 seconds (control, 18 seconds). Serum albumin (November 3) was 3.5 Gm. per 100 cc. and globulin 1.9 Gm. per 100 cc. Sputum cultures yielded hemolytic Staphylococcus aureus, coagulase positive. Electrocardiograms showed serial changes as in period A. The chest roentgenograms showed no change.

AUTOPSY

Gross Findings.—The body was that of a well developed and adequately nourished white man showing no external abnormalities other than pitting edema of the lower extremities and the abdominal wall and a barely perceptible degree of scleral jaundice. The peritoneal cavity contained approximately 1,000 cc. of a slightly turbid amber-colored fluid. The peritoneal serous surfaces were dulled but nevertheless smooth. The right pleural cavity held about 900 cc. of a clear transudate, and the left pleural space about 550 cc. of a similar fluid. There were a few small fibrous adhesions within the right cavity. The pericardial cavity was free of fluid but presented a picture of fibrin deposition.

The right lung weighed 450 Gm. and the left 400 Gm. In both upper lobes there was noted a number of nonaerated dense regions presenting a glassy appearance and colored a dark reddish

5 Duff, G., and Murray, E.: Bilateral Cortical Necrosis of the Kidneys, A. J. M. Sc. **201**:428-450, 1941.

black on cross section. Similar zones were demonstrable in the lower lobe of the left lung. The heart weighed 500 Gm. and showed an extraordinary degree of left eccentric hypertrophy. Dissection of the coronary arterial tree demonstrated complete atheromatous occlusion of the left anterior descending artery approximately 1 cm. beyond its origin. The remainder of the coronary vessels showed severe atherosclerotic change. The endocardium was normal in appearance except in the apical portion of the left ventricle, wherein several discrete salmon-colored mural thrombi were noted. Cross section of the myocardium at this point showed a considerable degree of thinning and fibrous tissue replacement. The gastrointestinal tract

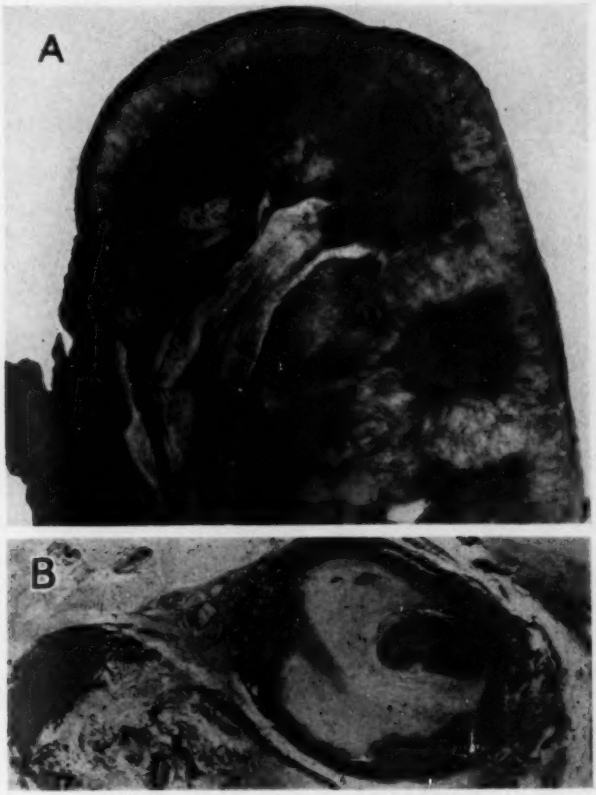

Fig. 1.—*A*, section of the right kidney showing no abnormalities. *B*, cross section of the midportion of the right renal artery demonstrating old atheromatous narrowing and recent complete thrombotic occlusion. Hematoxylin and eosin; × 6.5.

showed only a few small submucosal hemorrhagic patches in the ileum. The liver weighed 1,450 Gm. The surface was smooth. Cross section of the liver revealed only prominence of the lobular pattern. The gallbladder and tributary tree were grossly normal. No unusual features were noted grossly in the pancreas, the spleen, the adrenal glands or the pituitary gland.

Dissection of the renal arteries revealed complete occlusion of the right artery; the closure extended from the aortic orifice to within the parenchyma of the right kidney (fig. 1*B*). The contralateral renal artery was completely patent (fig. 2*B*). The right kidney weighed 190 Gm. The capsule was removed with ease. The surface of the right kidney and the parenchyma revealed

on transsection showed no abnormalities (fig. 1*A*). The right renal pelvis, ureter and ureteral orifice were normal. The left kidney was enlarged. The capsule was thickened and quite adherent to the underlying renal surface. The organ weighed 400 Gm. The revealed cortical surface exhibited a finely granular texture with a number of large yellowish depressed patches. Cross section of the organ (fig. 2*A*) demonstrated destruction of the cortex, this zone being replaced by a thin irregular layer of soft yellow granular tissue. A few such regions extended into the columns of Bertini. There was a thin hyperemic rim surrounding such areas of necrosis. The

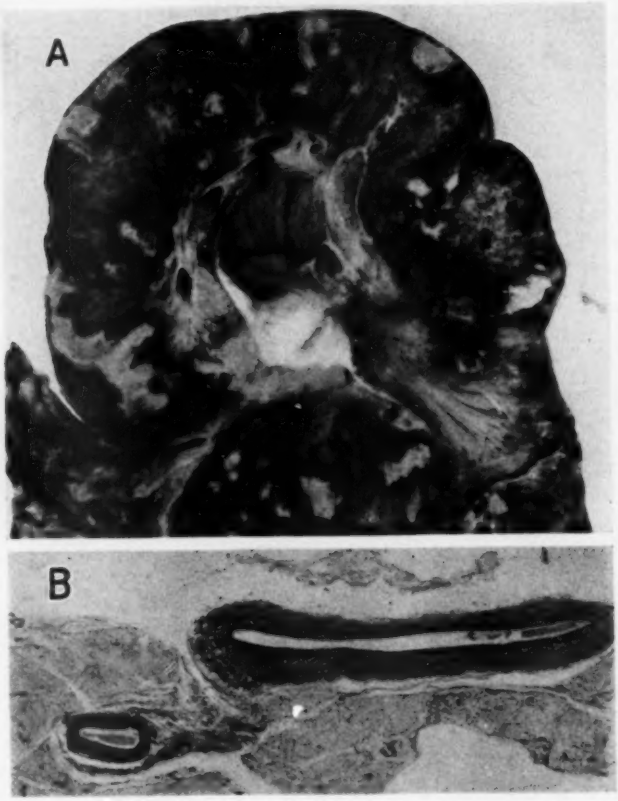

Fig. 2.—*A*, section of the left kidney showing zones of cortical necrosis rimmed by hemorrhage. *B*, cross section of the midportion of the left renal artery showing no abnormality. Hematoxylin and eosin; × 6.5.

renal pelvis on the left was normal except for the presence of submucosal ecchymoses. The left ureter was normal. The remainder of the genitourinary system demonstrated no abnormalities.

The rest of the gross examination, including dissection of the brain, revealed no abnormal conditions.

Microscopic Observations.—The myocardium in the region of fibrosis showed replacement fibrosis and subendocardial zones of acute myocardial necrosis with superimposed organizing mural thrombi. Sections from the lungs exhibited pneumonitis in varying stages of resolution. Other fields showed fibroblastic organization of the pneumonic process and marked chronic

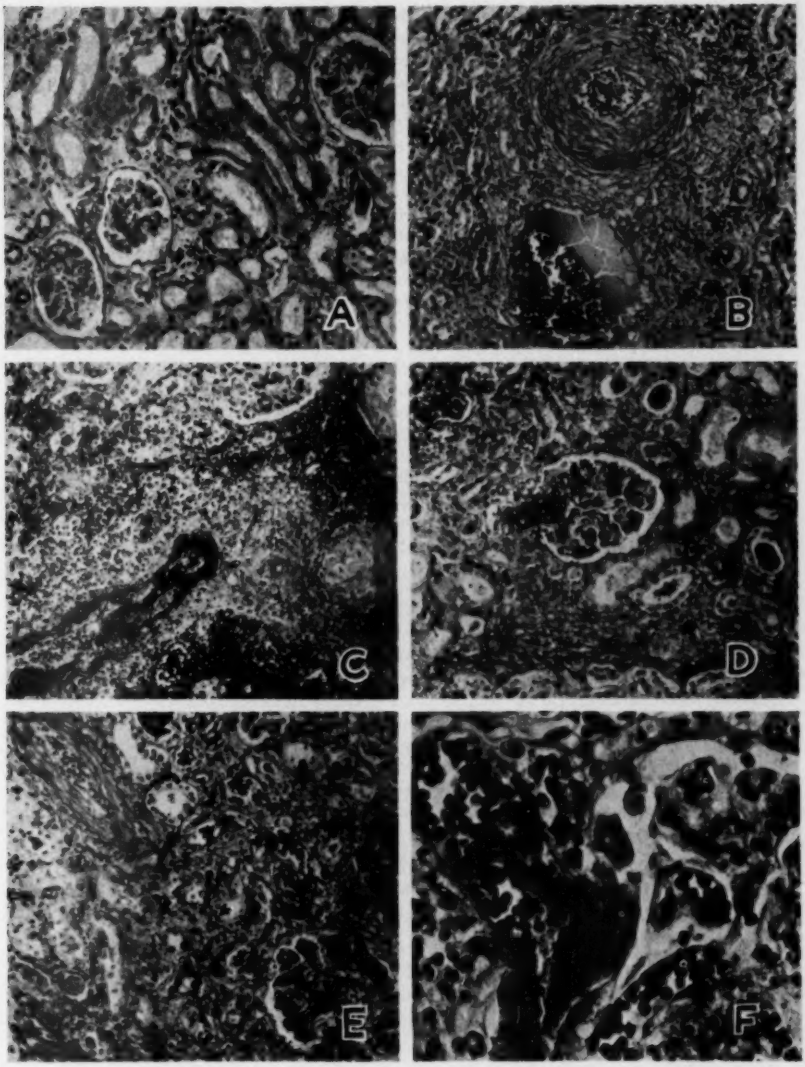

Fig. 3.—*A*, microscopic section of the right kidney revealing normal glomerular, tubular and vascular structures. Hematoxylin and eosin; × 100.

B, microscopic section of the left kidney showing severe intimal thickening within a small artery. Hematoxylin and eosin; × 100.

C, microscopic section of the left kidney demonstrating marked arteriolar necrosis as well as tubular degeneration and interstitial hemorrhage. Hematoxylin and eosin; × 100.

D, microscopic section of the left kidney showing severe fibrinoid degeneration of an afferent glomerular arteriole. Hematoxylin and eosin; × 100.

E, microscopic section of the left kidney presenting bland sclerosis of a small artery and degenerative tissue changes incident to the cortical necrosis. Hematoxylin and eosin; × 100.

F, microscopic section of the left kidney demonstrating fibrinoid masses partially occluding an afferent glomerular arteriole. Hematoxylin and eosin; × 475.

passive congestion and edema. The liver sections demonstrated central zonal congestion and hepatic cell necrosis. A number of these altered cells contained a yellowish brown pigment. Some of these larger zones of hepatitis tended to coalesce, leaving broad bands of acellular matrix. Sections of liver demonstrated, also, evidence of mild chronic passive congestion.

Sections of the right renal artery (fig. 1*B*) showed a considerable degree of subintimal atherosclerosis with pronounced narrowing of the lumen. Within the remaining lumen there was a recently formed, unorganized thrombus that completely closed off the passage. Multiple sections of the right kidney (fig. 3*A*) showed no unusual features. The arterioles and larger arteries were conspicuous by the absence of sclerotic changes. The glomeruli were normal in appearance except for one capillary loop showing a fibrinoid change.

The left renal artery showed no atherosclerosis microscopically (fig. 2*B*). Numerous microscopic sections of the left kidney demonstrated marked thinning of the cortex with confluent irregular areas of hemorrhagic necrosis, cloudy swelling and loss of nuclear detail, particularly in the tubular epithelial cells (fig. 3*C*). The medium-sized arteries showed a moderate degree of atherosclerotic thickening (fig. 3*B*). Many of the arterioles showed a bland hyaline type of intimal sclerosis (fig. 3*E*). The majority of the arterioles, including those in parenchymal areas uninvolved by necrosis, particularly the afferent glomerular branches, demonstrated a striking degree of acute eosinophilic mural necrosis, often with intramural or perivascular hemorrhagic and inflammatory cellular infiltration (fig. 3*C* and *D*). At times these vessels appeared completely occluded as the result of a fibrinoid degeneration and swelling of their walls. This degenerative process extended into the capillary glomerular loops, and entire glomerular segments exhibited a picture of alternating ischemia and congestion and necrosis (fig. 3*F*). Protein material and red blood cells were found in most spaces of Bowman. The tubules showed a nonspecific degenerative change which was not reflected in the medullary segments. The interstitial tissue of the cortex was filled with hemorrhage and foci of inflammatory exudate.

The remainder of the microscopic sections, including those of the pituitary and adrenal glands and the brain, showed no unusual lesions.

Summary of Pathological Diagnoses.—(1) Right renal artery atherosclerosis, severe, with recent superimposed thrombotic occlusion; (2) arteriolar sclerosis, benign hyaline type, of the left kidney, the pancreas and the liver; (3) accelerated (malignant) arteriolar nephrosclerosis, left kidney; (4) acute cortical necrosis, severe, left kidney; (5) fibrinous pericarditis; (6) old coronary occlusion, left anterior descending artery; (7) myocardial infarction, old and recent, left anterior wall, with superimposed mural thromboses; (8) cardiac hypertrophy; (9) ascites, bilateral hydrothorax; (10) organizing and resolving pneumonitis, left upper lobe, right upper lobe, left lower lobe; marked chronic passive congestion and edema of the lungs; (11) hepatitis (viral type), severe; (12) chronic passive congestion of the liver, mild.

COMMENT

It has been Goldblatt's [1] contention that in animals narrowing of only one renal artery is insufficient to cause anything more than transient hypertension. If, however, he greatly constricted the renal artery of one kidney and ligated the contralateral ureter, severe hypertension accompanied with renal insufficiency ensued. Malignant arteriolar lesions were demonstrable in the kidney with ureteral obstruction but not in the opposite kidney in which the renal artery had been constricted. On the basis of these findings, it was concluded that renal damage of some sort, in conjunction with hypertension, was requisite for the initiation of vascular lesions *within* the damaged kidney.

Wilson and Byrom,[6] working with rats, were able to produce sustained elevated blood pressures by severe occlusion of but one renal artery. In a significant number of their animals microscopic lesions indistinguishable from those of malignant nephrosclerosis in man were evident in the contralateral nonischemic kidney. They

6. Wilson, C., and Byrom, F. B.: Renal Changes in Malignant Hypertension; Experimental Evidence, Lancet **1**:136-139 (Jan. 21) 1939.

therefore postulated that these arteriolar necrotic changes were due to the vascular strain imposed by rapidly developing hypertension and that the ischemic kidney was protected from this vascular strain by the partial occlusion of its artery.

Saphir and Ballinger,[4] in perhaps the first paper on the subject of human unilateral malignant nephrosclerosis with contralateral renal lesions, concurred with Goldblatt in the opinion that some form of renal insufficiency was essential for the arterially nonobstructed kidney to exhibit malignant nephrosclerosis. In a review article on obstructive lesions of the renal artery, Yuile [2] presented a case of thrombotic occlusion of the left renal artery with a histologic picture of benign arteriolar nephrosclerosis in the contralateral kidney.

SUMMARY

A case of unilateral benign and malignant arteriolar nephrosclerosis and renal cortical necrosis in association with a contralateral atherosclerotic and thrombotic occlusion of the renal artery is presented. There is considerable similarity between the chronologically progressive narrowing of the right renal artery in the present case and the planned procedures of previous animal experimentation.

The evidence that in this case the hypertension was renal in origin (i. e., a consequence of ischemia of renal tissue) in no way warrants the conclusion that this is the exclusive or even the usual mode of production of human hypertension; but, rather, this is merely one of the mechanisms capable of its production.

The lesions of unilateral cortical necrosis in this case are expleined by the effects of a community of systemic and local alterations including (1) acute neurogenic vasospasm in the left kidney secondary to thrombosis of the contralateral renal artery,[8] (2) acute left cortical ischemia and anoxia resulting from explosive development of malignant arteriolar sclerosis in the left kidney and (3) diminished renal blood flow consequent to congestive failure.[9] It is believed that all these contributed toward renal vasospasm and compromise of the cortical blood flow in the left kidney, resulting in acute, severe anoxia of the left renal cortex, followed by necrosis. Acute, severe cortical anoxia is considered to be the common denominator between this case and those reported cases in which shock has been imputed as the cause of renal cortical necrosis.[10]

The immunity, in this case, of the contralateral (right) kidney to cortical necrosis is unexplained. We may theorize that this maintenance of tissue integrity in the right kidney can be accounted for by a combination of factors, viz., a direct cortical circulation derived principally from capsular vessels, a markedly diminished oxygen need secondary to the occlusion of its artery, and the absence of antecedent vascular damage in the right kidney.

The Medical Illustration Laboratory assisted in preparing the photographic plates.

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POSSIBLE EFFECTS OF HYPERSPLENIC EXTRACTS ON THE HEMOPOIETIC ORGANS OF MICE

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HYPERSPLENISM or abnormal splenic activity has assumed an important role in present day hematologic concepts. The spleen, apparently physiologically unimportant except for its reservoir function and lymphocytic content, has now become of much greater interest through the effect which splenectomy has on the hemogram in various primary and secondary blood dyscrasias. Beginning with Kaznelson's [1] successful splenectomies in instances of chronic Werlhof's disease and his empirical analogies with hemolytic anemia, the spleen has come to be regarded as the pathologic agent in the production of erythrocytopenia, neutrocytopenia and thrombocytopenia in various selected instances. The culmination of these hypotheses is evidenced in the recent description of a syndrome of "primary splenic hematopenia" (Doan and Wright [2]). In this symptom complex the splenic macrophages are strongly incriminated in the reduction of any one or all of the essential elements of the blood passing through this organ. However, the possibility that there is in the spleen some diffusible substance which might exert a hormonal-like effect was suggested, among others, by Lauda [3] in 1933 when he observed a reduction of the bleeding time following the injection of extracts of spleens. Perhaps the first detailed experimental attempt along this line was that of Torrioli and Pusic,[4] who injected large doses of a protein-free aqueous extract of a normal spleen intravenously into rabbits and thereby greatly reduced the peripheral blood platelet count. Earlier work by Torrioli and Puddu [5] demonstrated that splenic extracts prepared from the spleens of patients with idiopathic thrombocytopenic purpura injured in vitro megakaryocyte cultures of the bone marrows of guinea pigs. During the succeeding years (1938 to 1942) many attempts were made to corroborate or negate these findings. Starting with Troland

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1. Kaznelson, P.: Wien. klin. Wchnschr. **29**:1451-1454, 1916.

2. Doan, C. A., and Wright, C. S.: Blood **1**:10-26, 1946.

3. Lauda, E.: Die normale und pathologische Physiologie der Milz, Berlin, Urban & Schwarzenberg, 1933, pp. 226-271.

4. Torrioli, M., and Pusic, G.: Boll. Soc. ital. biol-sper. **9**:662, 1934.

5. Torrioli, M., and Puddu, V.: Policlinico (sez. med.) **41**:245, 1934; Recent Studies on Pathogenesis of Werlhof's Disease, J. A. M. A. **111**:1455-1456 (Oct. 15) 1938.

and Lee,[6] who used three thrombocytopenic purpura extracts and worked on three rabbits, one cat, one dog and one monkey, there have been 14 papers published in the English language in which seven investigators reported positive findings, six negative results and one a variable conclusion. If the authors of the present paper and the Italian workers are included in the experimental evaluation, the score stands nine positive and six negative. A more detailed study of the above results is presented later on in this paper with a possible causal analysis of the negative findings. Since the results of the other investigators have been questioned somewhat, leaving the etiology of idiopathic thrombocytopenic purpura still inconclusive, an attempt was made to repeat these experiments, using smaller animals and greater numbers than previously. Control studies were performed, using an extract of normal spleen. Because of the controversy still existent regarding the specificity of certain splenic extracts in the production of thrombocytopenia in experimental animals, an extract of the spleen of a patient with chronic splenic neutropenia was also used.

Sternal Myelogram of Patient 1

Myeloblasts	1.4%	Normoblasts	25.2%
Progranulocytes	4.2%	Erythroblasts	6.4%
Neutrophilic myelocytes	13.4%	Megaloblasts	0.6%
Eosinophilic myelocytes	1.3%	Megakaryocytes	0.8%
Neutrophilic metamyelocytes	24.8%	Erythroid total	33.09%
Eosinophilic metamyelocytes	0.6%	Myeloid-erythroid ratio = 67:33 = 2:1.	
Polymorphonuclear neutrophils	19.8%	Impression: normoblastic hyperplasia consistent with chronic bleeding associated with essential type of thrombocytopenic purpura; megakaryocytes are agranular but not increased in number (fig. 1).	
Polymorphonuclear eosinophils	0.6%		
Smudges	1.0%		
Myeloid total	67.0%		

REPORTS OF CASES IN WHICH EXTRACTS OF SPLEEN WERE OBTAINED

Sufficient clinical and hematological data are presented below to establish the accuracy of the clinical diagnoses of the cases in which the splenic extracts were prepared.

CASE 1 (Patient with Essential Thrombocytopenic Purpura).—N. L. H., a 23 year old white woman, was admitted to the Norton Memorial Infirmary on Feb. 9, 1947, complaining of metrorrhagia, ecchymoses, occasional epistaxes and bleeding gums. These hemorrhagic episodes occurred spontaneously and intermittently at first; subsequently they became continuous. Menadione, ascorbic acid, sulfonamide and penicillin preparations were administered, with negative results. (The gynecologic-obstetric history was irrelevant.) There was no history of preceding infection or drug ingestion, and the physical examination revealed a weak, pale young woman with blood pressure 110/80, temperature 98 F., pulse rate 100 and regular, and respiratory rate 24. Ecchymoses and hematomas (4 to 6 cm. in diameter) were observed over the entire body surface with exception of the face. The right nares showed recent hemorrhagic crusts; the nasopharyngeal, gingival and palatal mucosa contained numerous petechiae. Liver, kidney and spleen were not palpable. Roentgenograms of the chest and electrocardiograms revealed no abnormalities. The Kahn test was negative. On entrance the erythrocyte count was 2,820,000 per cubic millimeter; the hemoglobin content, 7.5 Gm. or 50 per cent (Haden-Hausser); the color index, 0.91; the white blood cell count, 4,500 per cubic millimeter (64 per cent segmented and 36 per cent nonsegmented granulocytes—no

6. Troland, C. E., and Lee, F. C.: Thrombocytopen: Substance in Extract from Spleen of Patients with Idiopathic Thrombocytopenic Purpura That Reduces the Number of Blood Platelets, J. A. M. A. **111**:221-226 (July 16) 1938.

abnormal cells seen); thrombocytes, 28,300 per cubic millimeter (Rees-Ecker method—checked by Fonio method nine days after admission, 40,000 per cubic millimeter); clot retraction (Lee-White method), none at end of three hours and beginning clot formation at end of four hours; bleeding time (Duke method), 9 minutes; coagulation time (Sabraze capillary tube method), 5 minutes; prothrombin time (Smith modification of Quick method), 125 per cent of normal; tourniquet test, positive. Marrow obtained by puncture of the sternum one day after admission revealed the cellular composition shown in the adjoining myelogram.

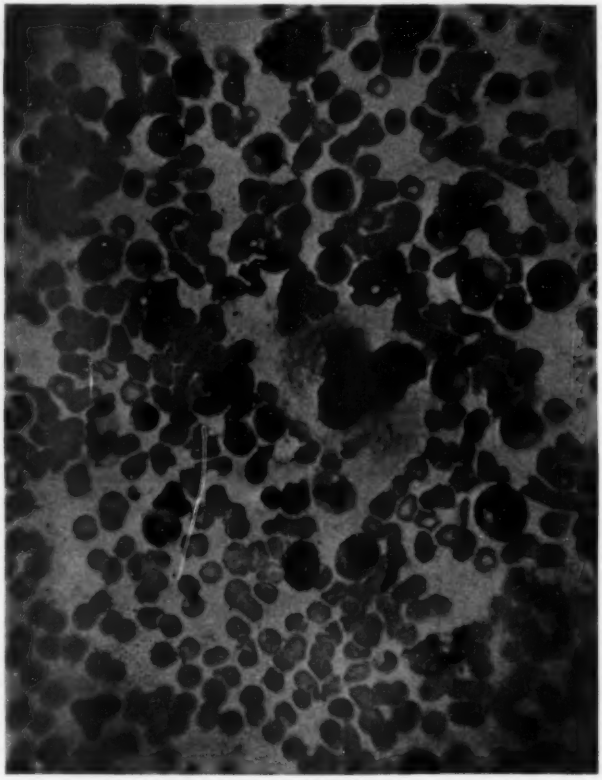

Fig. 1 (case 1).—Sternal marrow imprint (presplenectomy; patient had essential thrombocytopenic purpura). Note bizarre, nucleated, centrally located megakaryocyte with agranular cytoplasm. Wright's stain; × 470.

The patient was splenectomized 12 days after admission. The thrombocyte count was 300,000 per cubic millimeter three days after operation and 340,000 seven days after operation. All other hematological findings were essentially normal. The spleen was bluish red, of firm consistency, and weighed approximately 165 Gm. On cut section, the malpighian corpuscles appeared as grayish ovoid bodies measuring 2 to 4 mm. in diameter. The capsule was not thickened, and no accessory spleniculi were observed. Microscopic study revealed hyperplastic malpighian corpuscles, some fused with one another. An occasional central arteriole showed subintimal hyalinization. The splenic pulp presented an apparent increase in fibrous elements, eosinophils, polymorphonuclear neutrophils, mononuclear cells and large cells

with eosinophilic amorphous cytoplasm and multiple vesicular irregular nuclei. The latter cells resembled megakaryocytes. There was also slight phagocytosed blood pigment within the pulp spaces. These findings were consistent with the pathologic changes occasionally observed in the spleens of essential thrombocytopenic purpura.

CASE 2 (Patient with Primary Splenic Neutropenia).—K. L. M., a 42 year old white woman, was admitted to the Norton Memorial Infirmary on Feb. 20, 1947, complaining of weakness and a progressively enlarging mass in the left side of the abdomen of three years' duration. There was no history of icterus or hematemesis. A review of systems gave essentially negative results except for delivery of a 6 month stillborn fetus in August 1946. Physical examination showed a temperature of 98.4 F., a pulse rate of 85, a respiratory rate of 20 and a blood pressure of 120/80. There was no abnormal finding other than a palpable mass in the left upper quadrant of the abdomen, extending 3 fingerbreadths below the left costal margin and reaching to the level of the umbilicus medially. A right partial foot drop was also present (first observed following the above described delivery). On admission the red blood cell count was 4,360,000 per cubic millimeter, the hemoglobin content 12.5 Gm.

Sternal Myelograms of Patient 2

	Preoperative	Postoperative (23 days after splenectomy)
Normoblasts	40.8%	15.8%
Erythroblasts	6.4%	3.0%
Megakaryocytes	1.2%	0.4%
Erythroid total	48.4%	19.2%

	Preoperative	Postoperative (23 days after splenectomy)
Myeloblasts	1.0%	3.8%
Progranulocytes	2.0%	4.8%
Neutrophilic myelocytes	13.6%	16.4%
Eosinophilic myelocytes	1.0%	0.6%
Neutrophilic metamyelocytes	25.6%	12.4%
Eosinophilic metamyelocytes	1.2%	0.0%
Polymorphonuclear neutrophils	6.8%	32.4%
Polymorphonuclear eosinophils	0.0%	7.6%
Lymphocytes	0.4%	2.8%
Myeloid total	51.6%	80.8%
Myeloid-erythroid ratio = 2:2	Myeloid-erythroid ratio = 4:1	
Impression: erythroid hyperplasia with slight myeloid depression.	Slight myeloid hyperplasia with increased polymorphonuclear maturation.	

(83.3 per cent), the color index 0.9; the white blood cell count was 1,600 per cubic millimeter (68 per cent segmented and 30 per cent nonsegmented), and the thrombocyte count, 120,000 per cubic millimeter. The specific gravity of the urine was 1.016 (otherwise the urine was normal). In an erythrocyte fragility test, initial hemolysis was at 0.42 per cent, complete hemolysis at 0.32 per cent, and a control the same. The reticulocyte count was 0.67 per cent. The erythrocyte sedimentation rate (Cutler method) was 16 mm. at the end of one hour; the hematocrit showed 41 mm. in one hour; the volume index was 1.06. The total serum protein (Van Slyke method) was 6.7 Gm. (albumin 3.9 per cent, globulin 2.8 per cent, ratio 1.4:1). An agglutination test for Brucella abortus was negative. A test for Rh factor was positive. The Kahn test was negative. Roentgen study of the chest and extremities showed no abnormality. An electrocardiogram revealed sinus tachycardia with slight left axis shift.

The preoperative bone marrow findings (see accompanying myelograms of patient 2) are consistent with those described by Doan as occasionally encountered in a myelogram showing normal or slightly hyperplastic marrow associated with primary splenic neutropenia. Twenty-four hours after the removal of the spleen the white blood cell count was 13,650 per cubic millimeter (68 per cent segmented cells, 11 per cent band cells and 1 per cent eosinophils); forty-eight hours after splenectomy the white blood cell count was 19,900 per cubic millimeter with a relatively normal differential count. Gross examination of the spleen revealed a 1,200 Gm.

firm specimen with a smooth, regular capsule. Three accessory spleniculi were also present; each measured 1 by 1 cm. in diameter. On cut section the malpighian bodies were indistinct. Microscopically, the sinusoids were somewhat thickened. The pulp space showed sequestration of polymorphonuclear granulocytes with occasional mononuclear cells. The malpighian bodies showed moderate hyperplasia of the germinal centers. Oil immerson examination revealed phagocytosis of mature and degenerating polymorphonuclear neutrophils by the macrophages and reticulum cells of the splenic pulp. The histopathological observations were thought to be consistent with those observed in primary splenic neutropenia[7] (fig. 2).

Case 3 (Patient with Normal Spleen [Control]).—M. R., a 21 year old man, was admitted to Norton Memorial Infirmary on March 7, 1947 with a chief complaint of dysphagia and regurgitation of food since birth. At his fifth year of age a diagnosis of pyloric stenosis was made and a gastroenterostomy performed. He was symptomless for one week after the

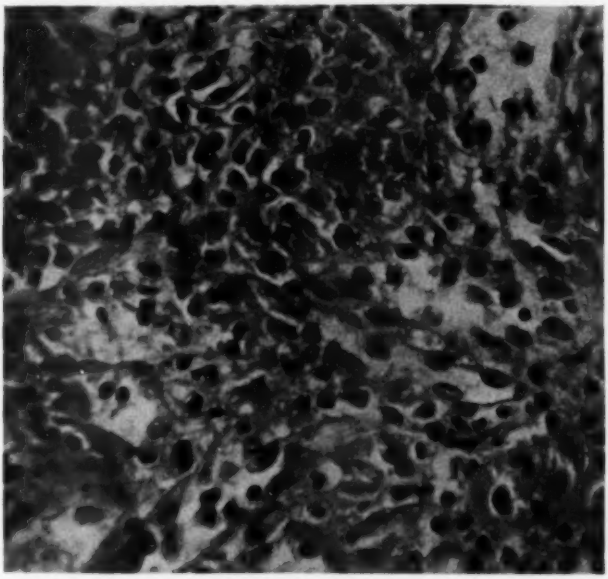

Fig. 2 (case 2).—Spleen of patient with primary splenic neutropenia. Note sequestration and phagocytosis of polymorphonuclear granulocytes. Hematoxylin and eosin; × 470.

operation, but when he was started on solid food, his symptoms recurred. Since then, esophageal bougies had been passed at intervals of six to eight weeks. The patient had maintained his nutrition on soft chopped foods and liquids. On admission the pulse rate was 120, the respiratory rate 22, the temperature 98.6 F. and the blood pressure 110/70. Physical examination disclosed only a healed paramedian scar and a drainage scar in the left posterior midscapular line in the tenth intercostal space from an old empyema following pneumonia. Laboratory findings were essentially negative—a red blood cell count of 4,640,000 per cubic millimeter, a hemoglobin content of 14.0 Gm. (93.3 per cent), a color index of 1.01, a white blood cell count of 5,600 per cubic millimeter (66 per cent neutrophils, 2 per cent eosinophils, 4 per cent monocytes, 28 per cent lymphocytes), a negative Kahn test, a normal urine. Preoperative roentgen examination revealed a congenitally short esophagus with a stricture present

7. Wiseman, B. K., and Doan, C. A.: Ann. Int. Med. **16**:1097-1117, 1942.

at the esophageal-gastric junction. Operation showed a congenitally short esophagus which joined the thoracic stomach midway between the pulmonary vein and the diaphragm. Splenectomy was considered necessary in order to mobilize further the greater curvature of the stomach for an esophagoplasty. The spleen weighed 100 Gm. and was normal in color and consistency, and microscopic examination revealed no abnormal change.

PREPARATION OF EXTRACTS

In every case described above the spleen was prepared for extraction within 30 minutes after splenectomy. Extraction was carried out according to the original procedure outlined by Troland and Lee.[6] Briefly, each spleen was weighed and then placed in a medium fine meat grinder. The ground splenic tissue was deposited in dark brown glass gallon containers and mixed with a volume of commercial acetone equal to five times the weight of the tissue. The containers were then sealed and permitted to remain at room temperature for approximately four months, being gently agitated at least once a day during that time. After extraction was completed, the mixtures were placed, separately and individually, in large cylindric containers and allowed to evaporate at room temperature. (It was thought that even a small amount of heat might affect the chemical structure and potency of the preparation.) This required approximately 36 to 48 hours each. The resulting residue was brown and gummy. Distilled water was added and the suspension thoroughly shaken, the final solution containing approximately 1 Gm. of splenic tissue per cubic centimeter of extract. These suspensions were then filtered, first through coarse filter paper and then through fine Seitz filters, into an attached sterile suction flask. Approximately 2 cc. of light brown clear fluid was removed aseptically from each flask for aerobic and anaerobic culture studies. Forty-eight and 72 hour observations were recorded. When these proved to be negative, 0.3 cc. of 1 : 1,000 aqueous thimerosal N. F. (merthiolate®) was added, and the solutions were then placed in previously sterilized autoclaved vaccine bottles and refrigerated at 10 C. Before actual animal inoculations were made, bacteriologic studies were again made. The results were continuously negative. Since 20 cc. of similarly prepared extracts had been injected into approximately 2-Kg. rabbits by other authors, we decided to use comparative amounts per ratio body weight in our mice (averaging 28 Gm. each). Three strains (Swiss, C 57 and A) were used in order to eliminate any possibility of strain variation in response. One hundred animals were selected. Ten control mice (four Swiss, three C 57 and three A strain) were selected and studied over a one week period with serial analyses of the red blood cell count, the hemoglobin content, the white blood cell count, the differential white cell count, the thrombocyte count, the reticulocyte percentage, the bleeding and coagulation times and finally the femoral marrow surveys. The femoral marrow was removed and smeared immediately after the death of each animal. The remaining 90 mice were divided into three groups (10 Swiss, 10 C 57 and 10 A strain mice, in each group). Since no significant variation was found in the peripheral blood and marrow studies of these varieties of mice, blood studies were made 2, 5, 10, 15, 20, 24, 30, 35, etc., hours after intraperitoneal injection of 0.2 cc. of the various splenic extracts. In one group (different in each splenic extract series of injections of mice) the inoculations were repeated at the end of 24 and 48 hours and a hemopoietic study made at the end of 72 hours (fig. 3). Blood was obtained by cutting the tip of the tail with a sharp small scissors (the tail having been previously cleansed with alcohol and the animal having been kept completely quiet in a cellophane mouse container prepared with a breathing hole at one end and a notched cork at the other end for the tail). All blood studies were made by one person using the same technics throughout. Thrombocyte counts were performed, the method of Rees and Ecker being used, checked by the indirect Wright stained smear technic. Terminal blood studies were made from heart blood in some cases, and this blood did not show significant variations when compared with tail blood. Bleeding time was determined by the Duke method; coagulation time, by the capillary tube method, and reticulocyte counts were made by using the cresyl blue, cover glass supravital technic. Immediately after the death of the animals, the internal viscera were removed and placed in formaldehyde solution U. S. P. diluted 1 : 10. The femur was then fractured, and femoral marrow imprints were made and stained, the Wright procedure being used.

RESULTS

The values obtained by examination of the peripheral blood of the control (nontreated) series of mice compared favorably with those of similar studies made by Scarborough [8] in the same animal group. The erythrocyte count of the A strain averaged 9,030,000 red blood cells per cubic millimeter; hemoglobin content, 14.0 Gm. (93.3 per cent); color index, 0.55; hematocrit value, 50 mm.; reticulocyte percentage, 0.28; total leukocyte count, 7,850 per cubic millimeter (differential count, 56 per cent lymphocytes, 11 per cent monocytes, 31 per cent neutrophils, 2 per cent eosinophils); thrombocyte count, 389,000 per cubic millimeter; bleeding

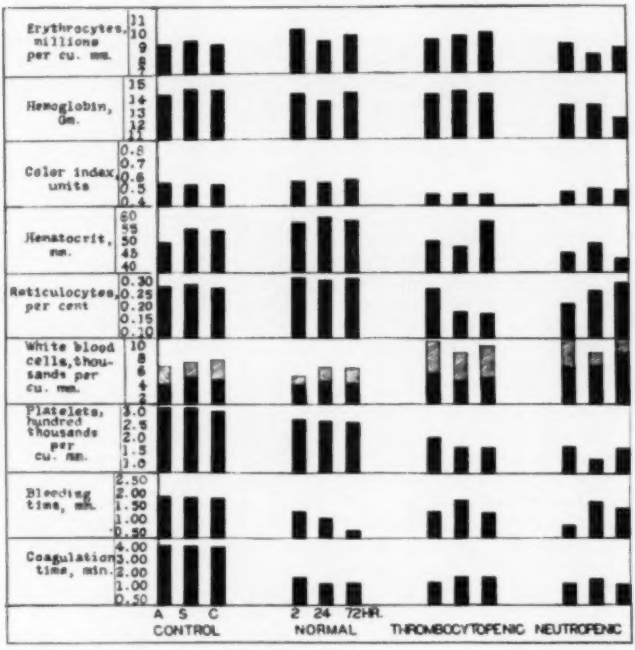

Fig. 3.—Graphic presentation of hemograms of mice which had received intraperitoneal injections of splenic extracts. *A*, *S* and *C* controls are A strain, Swiss strain and C 57 strain mice, respectively. In the section on white blood cell counts, the diagonally striped portion of the column represents segmented granulocytes; the solid black portion, nonsegmented granulocytes.

time, 2 minutes, 15 seconds; coagulation time, 4 minutes, 20 seconds. Second analyses of the Swiss (S) and C 57 (C) strain showed similar average findings (fig. 3). Intraperitoneal injection of 0.2 cc. of extract prepared from the thrombocytopenic purpura spleen of case 1 produced the final average results depicted in figure 3. A break-down analysis of this chart shows practically no change in the erythrocyte and hemoglobin levels; a slight reduction in the color index from 0.55

8. Scarborough, R. A.: Yale J. Biol. & Med. **3**:63, 168, 282, 359 and 547, 1931.

to 0.45 with a concomitant 5 mm. increase in the hematocrit values in the 72 hour observation; a comparable reduction in reticulocyte percentage from 0.28 to 0.18 was observed 24 and 72 hours after extract injection (apparently nonspecific since it cannot be correlated with any erythroid depression as evinced from a study of the femoral myelograms—see myelograms of mice). The total white cell count also shows an apparent (nonspecific) variation in its over-all increase, especially in the neutrophilic series. It is difficult to base this rise on splenic tissue inoculation per se, since it was also observed in the neutropenic extract series findings and not noted in the normal splenic extract group hemograms. However, bone marrow studies do not reveal concomitant myeloid hyperplasia (see myelograms of mice). The thrombocyte findings were, perhaps, the most interesting in this injection group. It will be noted that there was a significant increasing diminution in the total number of thrombocytes starting from the injection of the extract of

Femoral Myelograms (Average Findings) of Mice Receiving Intraperitoneal Injections of Splenic Extracts

	N.	T.P.	S.N.
Blasts	1.6	2.8	1.4
Progranulocytes	2.0	1.2	0.8
Neutrophilic myelocytes	4.2	3.0	1.4
Eosinophilic myelocytes	0.8	1.2	2.0
Neutrophilic metamyelocytes	5.2	4.0	2.2
Eosinophilic metamyelocytes	0.2	0.4	0.6
Polymorphonuclears	49.0	46.8	26.0
Monocytes	0.2	0.0	0.0
Eosinophils	1.4	1.2	1.4
Lymphocytes	1.4	0.8	0.6
Smudges	2.4	4.8	1.4
Myeloid	66.4	66.2	37.8
Normoblasts	24.4	24.0	59.0
Erythroblasts	4.4	6.8	1.6
Megakaryocytes	0.8	0.6	0.2
Reticulum cells	2.0	2.4	1.4
Erythroid	31.6	33.8	62.2

N. = normal splenic extract.
T.P. = thrombocytopenic purpura splenic extract.
S.N. = splenic neutropenia splenic extract.

normal spleen and continuing through the other two splenic extract injections—that is, a steplike decrease from 389,000 (control) to 292,000 (normal splenic extract) to 160,000 thrombocytes per cubic millimeter (thrombocytopenic splenic extract series) (fig. 3). Examination of figure 4 shows that the latter extract induced a typical response, i. e., a maximal progressive reduction in platelets at the end of 24 hours with a gradual return to 410,000 per cubic millimeter after 65 hours. In occasional animals the thrombocyte reduction lasted as long as four to six days and then returned to normal levels over a subsequent 18 to 48 hour period. The bleeding times remained within normal limits (1.5 to 2.0 minutes). No petechiae or purpuric manifestations were observed in any of the organs grossly or microscopically. The coagulation time averaged 1.8 to 2 minutes in all splenic injection series as compared with the control average level of 4 minutes, 20 seconds. Femoral myelograms revealed a myeloid-erythroid ratio of 66.2:33.8 (approximately 2:1). No abnormal cells were observed with regard to either quality or quantity. The visceral organs with the exception of the spleen and the lung were not remarkable. Microscopically the spleen showed a definite quantitative increase

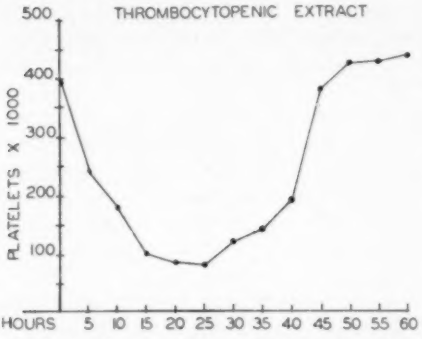

Fig. 4.—Average platelet level response in mice following intraperitoneal injection of essential thrombocytopenic purpura splenic extract.

Fig. 5.—Spleen of mouse which had received an intraperitoneal injection of essential thrombocytopenic purpura extract. Note quantitative increase in the number of megakaryocytes. Hematoxylin and eosin stain; × 470.

in the number of megakaryocytes (fig. 5). The cytoplasm therein was relatively agranular, and only an occasional thrombocyte was seen. The lungs also showed a definite increase in these precursors of thrombocytes; the megakaryocytes were located in dilated capillaries of alveolar walls (fig. 6).

Intraperitoneal injection of 0.2 cc. of extract prepared from the primary splenic neutropenia spleen of case 2 produced the final average results depicted in figure 3. A critical survey of this chart shows erythrocyte and hemoglobin values which do not vary significantly from those obtained in the control series. The color index

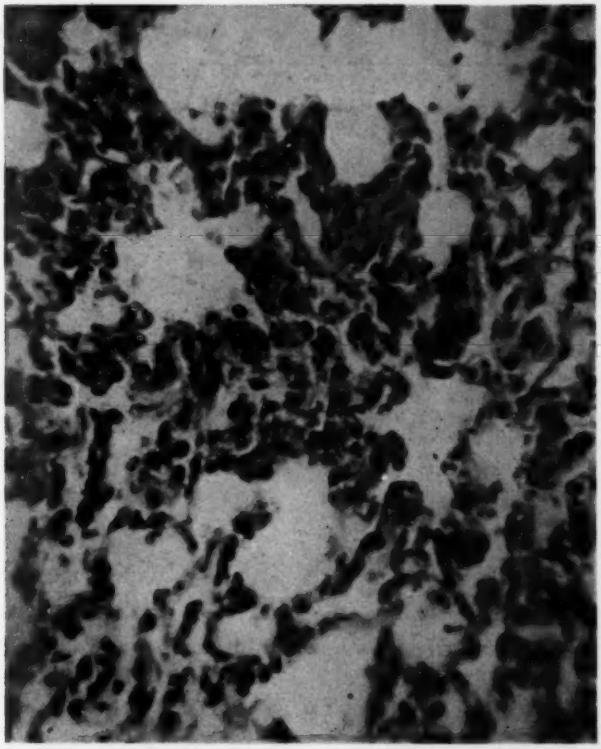

Fig. 6.—Lung of mouse which had received an intraperitoneal injection of essential thrombocytopenic purpura extract. Note definite increase in megakaryocytes in alveolar capillaries. Hematoxylin and eosin stain; × 470.

varied from 0.48 to 0.5 unit with a decrease in the hematocrit levels from 55 mm. (control) to 44-48 mm.; the reticulocyte percentage varied from 0.20 to 0.30, the higher values being obtained at the end of 72 hours. The total leukocyte levels showed insignificant variations ranging from averages of 9,550 to 12,150 white blood cells per cubic millimeter, with differential counts displaying approximately normal proportions of segmented and nonsegmented cells (lymphocytes 63 per cent, monocytes 2 per cent, segmented granulocytes 35 per cent). The platelet quantities

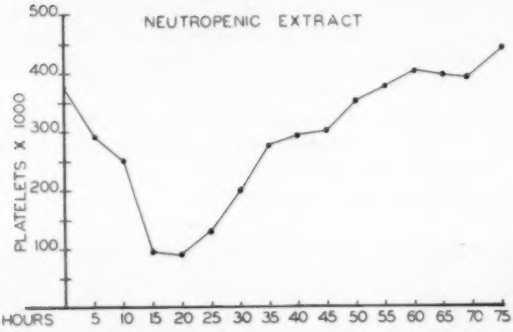

Fig. 7.—Average thrombocyte level response in mice following intraperitoneal injection of primary splenic neutropenia splenic extract.

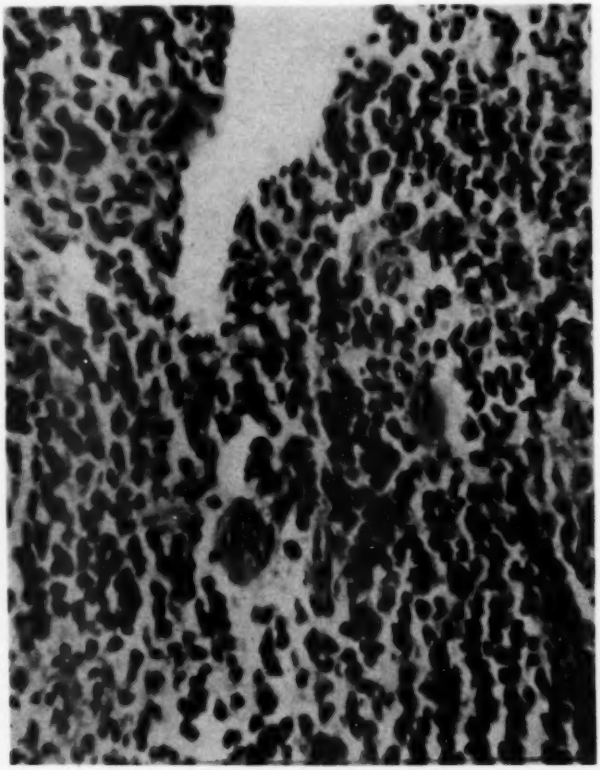

Fig. 8.—Spleen of mouse which had received an intraperitoneal injection of primary splenic neutropenic splenic extract. Note increase in atypical agranular megakaryocytes of the same type as those observed in figure 5. Hematoxylin and eosin stain; × 470.

per cubic millimeter decreased as described in the preceding experiment; i. e., at the end of 20 hours after the initial injection an average reduction from 376,000 per cubic millimeter to 70,000 was observed (fig. 7). This returned progressively to normal within 70 to 75 hours; on some occasions a reduction level was maintained over a three to five day period. There was no prolongation of the bleeding time (0.8 to 1.5 minutes) and no demonstrable gross evidence of purpura on examination of the animals' viscera. An average coagulation time of 1.8 to 2 minutes was noted. An interesting observation (though inexplainable from the above peripheral blood findings) made on the femoral marrow imprints was that of a reversal of the normal myeloid-erythroid ratio (i. e., M : E = 37.8 : 62.2 — approximately 1 : 2) (see myelograms of mice). Histopathologically, the spleen showed an increase in atypical megakaryocytes of the same type (fig. 8) as those described in the previous experiment.

Intraperitoneal injection of 0.2 cc. of the extract of the normal spleen of case 3 produced few hematological variations in the treated animals as compared with the control series. The erythrocyte, hemoglobin, color index, hematocrit and

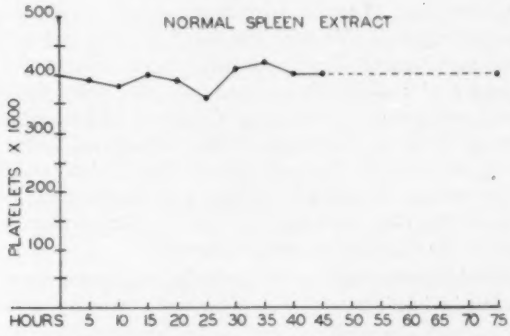

Fig. 9.—Average platelet level response in mice following intraperitoneal injection of normal spleen extract.

reticulocyte values averaged, respectively, 9,420,000 per cubic millimeter, 14.5 Gm., 0.57 unit, 56 mm. and 0.32 per cent. The leukocytes averaged 7,350 per cubic millimeter (63 per cent lymphocytes, 31 per cent neutrophils, 2 per cent eosinophils, 4 per cent monocytes); thrombocytes, 292,000 per cubic millimeter (very little variation noted on five hourly observations) (fig. 9). Bleeding time varied from 0.7 to 1.5 minutes; coagulation time, from 1.5 to 2 minutes. Femoral myelograms revealed a normal myeloid-erythroid ratio of 68.4 : 31.6 or approximately 2 : 1. No significant gross or microscopic visceral alterations were observed.

COMMENT

The possibility of the spleen functioning as an endocrine organ has been suspected for a long time.[9] However, in spite of a great deal of circumstantial evidence, there was no valid proof of an internal secretion of the spleen. In fact, the endocrine glands per se have a variable effect on the destruction of thrombocytes

9. Ungar, G.: Endocrinology **37**:329-340, 1945.

in the peripheral blood [10a]; e. g., in rats orchiectomy and ovariectomy are followed by thrombocytopenia, [10b] while after either adrenalectomy or the injection of extracts of sexual glands, there is thrombocytosis.[10c] Many inconclusive arguments have been proposed suggesting hypersplenism on a hormonal basis as the causative factor in the production of the platelet depression associated with idiopathic thrombocytopenic purpura. For example, many surgeons have made the observation that at the time of splenectomy the abnormal oozing of blood frequently stops abruptly when the splenic pedicle is clamped in spite of the fact that the number of thrombocytes in the peripheral blood remains unchanged at that time; therefore, the effect on hemostasis could be due to some substance or substances in the blood other than the platelets. In fact, according to Nickerson and Sunderland,[11] thrombocytopenia is not the sole factor in the causation of hemorrhages. These authors are unable to say whether there is a concomitant qualitative defect of the platelets or a capillary hyperpermeability or both. However, the correlation between the bleeding tendency and the platelet level is so close one feels that the thrombocyte must indeed be at least one important factor in the purpuric manifestations of Werlhof's disease.

Up to the present time 14 papers have been published in the English language in which seven investigators (Troland and Lee,[9] Hobson and Witts,[12] Otenasek and Lee,[13] Rose and Boyer,[14] Paul,[15] Cronkite [16] and Moolten [17]) have demonstrated the presence of a diffusible substance obtained from acetone extracts of spleens of patients splenectomized because of diagnosed idiopathic thrombocytopenic purpura. Six other workers (Pohle and Meyer,[18] Major and Weber,[19] Tocantins,[20] Hodge and Strong,[21] Wiseman, Doan and Wilson [22] and Colmer and Mersheimer [23]) obtained negative results. Uihlein's [24] findings were variable and inconclusive. A detailed analysis of the data published by these workers indicates the following possible reasons for the six negative results obtained [13]:

1. The extractable factor may be thermolabile, and hence some of its potency may have been lost by heating.

10. (*a*) Tocantins, L. B.: Medicine **17**:155-260, 1938. (*b*) Bankow, G.: Beitr. z. path. Anat. u. z. allg. Path. **88**:113-126, 1931. (*c*) Shecket, H. A.; Friedman, D. L., and Nice, L. B.: Proc. Soc. Exper. Biol. & Med. **32**:608-610, 1935.

11. Nickerson, D. A., and Sunderland, D. A.: Am. J. Path. **13**:463-489, 1937.

12. Hobson, F. C. G., and Witts, L. J.: Brit. M. J. **1**:50-51, 1940.

13. Otenasek, F., and Lee, F. C.: J. Lab. & Clin. Med. **26**:1266-1273, 1941.

14. Rose, H., Jr., and Boyer, L. B.: J. Clin. Investigation **20**:81-86, 1941.

15. Paul, J. T.: J. Lab. & Clin. Med. **27**:754-762, 1942.

16. Cronkite, P.: Ann. Int. Med. **20**:52-62, 1944.

17. Moolten, S. E.: J. Mt. Sinai Hosp. **12**:866-873, 1945.

18. Pohle, F. J., and Meyer, O. O.: J. Clin. Investigation **18**:478, 1939.

19. Major, R. H., and Weber, C. J.: J. Lab. & Clin. Med. **25**:10-13, 1939.

20. Tocantins, L. M.: Proc. Soc. Exper. Biol. & Med. **42**:485-486, 1939.

21. Hodge, I. G., and Strong, P. T.: Bull. Ayer Clin. Lab., Pennsylvania Hosp. **3**:267-276, 1939.

22. Wiseman, B. K.; Doan, C. A., and Wilson, S. J.: Present Status of Thrombocytopenic Purpura with Special Reference to Diagnosis and Treatment, J. A. M. A. **115**:8-13 (July 6) 1940.

23. Colmer, M. L., and Mersheimer, W. L.: Relation of Splenic Extract to Etiology of Essential Thrombopenia, Arch. Surg. **43**:422-426 (Sept.) 1941.

24. Uihlein, A.: J. Lab. & Clin. Med. **28**:157-162, 1942.

2. Bacterial and other contamination could have produced an antagonistic specific [25] as well as nonspecific effect. Therefore, as an added precaution, Seitz filtration should be carried out before injections.

3. The potency of the extracts, as preserved in aqueous solution, might have diminished with time.

4. Several forms of idiopathic thrombocytopenic purpura, depending on the size of the spleen and the presence or the absence of an extractable platelet-reducing substance, might exist. (Clinically a large spleen has raised doubts regarding the correct diagnosis of thrombocytopenic purpura.)[26]

Finally, the detailed chemical extraction and bioassay of splenic tissue by Moolten,[17] as well as the significant histological findings, seem to favor hypersplenism conclusively as the basis for the thrombocytopenia occurring in cases of idiopathic thrombocytopenic purpura. He demonstrated that two steroid preparations exist in the spleen in comparative abundance and may be isolated in relatively concentrated form absorbed on cholesterol following crystallization of the latter from crude acetone-ether extracts, previously emulsified and dissolved in absolute methyl alcohol: One, a platelet-lowering lipid, was called "thrombocytopen"; the other, a platelet-elevating lipid, was called "thrombocytosin." An analysis of the bioassayed material suggests tentatively that in the human organism significant amounts of both thrombocytopen and thrombocytosin occur in the spleen, diminishing in amount with metaplasia or with repiacement of its functioning reticuloendothelial elements (hemosiderosis, Hodgkin's disease, leukemia). It therefore appears that the spleen exerts a dual control on the rate at which platelets are delivered into the circulating blood. Furthermore, after several days' administration of large doses of thrombocytopen a refractory state and "platelet escape" were observed. Simultaneously, the bone marrow revealed a remarkable hyperplasia of megakaryocytes, which were in various states of maturation. There were no significant changes in red blood cell or white blood cell counts. Purpura was not observed in any of the experiments with thrombocytopen although prolongation of bleeding time persisted for weeks subsequent to administering a large dose in peanut oil. Excessive agglutination of platelets [27] and clotting of blood in the counting pipet occurred in some experiments, with thrombocytosis at or near the peak of platelet rise; thromboses were not observed. Histologically, in purpura haemorrhagica the spleen may exhibit lipoidal vacuolation of the hyperplastic reticulum cells. When this microscopic pattern predominates thrombocytopen may be extracted in great quantity. On the other hand, thrombocytosin is apparently stored in subcutaneous adipose tissue, and its mobilization from traumatized fat cells may possibly explain elevations in thrombocyte count after surgical operations in general.[28] Both factors are also present in egg yolk,

25. Gunn, F. D.: Reactions of Bone Marrow in Experimentally Induced Thrombocytosis, Arch. Path. **12**:153-179 (Aug.) 1931.

26. Wiseman, B. K. in Forman, J.: A Review of Medical Progress, Being a Series of Addresses given at the Sixth Post-Collegiate Clinical Assembly, College of Medicine, Columbus, Ohio, Ohio State University, 1939, p. 174.

27. Fitzgerald, P. J.; Auerbach, O., and Frame, E.: Blood **2**:519-541, 1947. Singer, K.; Bornstein, F. P., and Wile, S. A.: Ibid. **2**:542-554, 1947.

28. Steiner, P. E., and Gunn, F. D.: Proc. Soc. Exper. Biol. & Med. **28**:1088-1093, 1931. Wright, H. P.: J. Path. & Bact. **54**:461-468, 1942. Adams, E.: Postoperative Thrombocytosis, Arch. Int. Med. **73**:329-335 (April) 1944.

thrombocytosin predominating and effective orally. The purified factors are apparently nontoxic, thrombocytosin being tentatively classified as a fat-soluble dietary factor and thrombocytopen as a fat-soluble hormone. Possible therapeutic applications suggest the use of thrombocytosin in certain cases of idiopathic or secondary thrombocytopenic purpura, and thrombocytopen in states of hypercoagulability of the blood, in thrombocythemias and possibly in vegetative endocarditis.

SUMMARY

Acetone extracts of spleens of patients with idiopathic thrombocytopenic purpura and chronic splenic neutropenia, which were tested in three strains of mice, appear to contain a thrombocytopenia-producing factor.

A reversal of the myeloid-erythroid ratio was observed in the femoral myelograms of mice receiving injections of splenic neutropenia extracts. No peripheral granulocytopenia was produced.

Histopathological evidence of megakaryocytoplasia was found in the lungs and the spleens of these three strains of mice.

An analysis and a possible explanation of the negative results obtained by six other workers in the field are presented.

In this experiment, at least, platelet-reducing factors in certain acetone extracts of spleen appear to be nonspecific.

HISTOLOGIC AND PERFUSION STUDIES OF THE UNMANIPULATED KIDNEY IN RABBITS WITH UNILATERAL RENAL HYPERTENSION

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AND
DOUGLAS R. DRURY, M.D.
LOS ANGELES

IN THE DOG ischemia of one kidney in the presence of the other normal kidney results in a moderate rise of blood pressure, but the arterial hypertension ordinarily does not last more than several weeks.[1a] The blood pressure falls promptly to normal if the ischemic kidney is removed during this period of hypertension.[1b] In the rat and in the rabbit the hypertension resulting from ischemia of one kidney in the presence of a normal kidney is much more enduring, and if in these animals one removes the ischemic kidney after a month or more of high pressure, the level does not fall to normal immediately, but may continue high for many weeks.[2] In searching for the change that is responsible for the persistence of the hypertension after removal of the causal kidney, the possibility of alteration in the other kidney comes quickly to mind.

This could be brought about by one of two mechanisms. The period of hypertension might bring about a thickening of the arterioles and

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1. Braun-Menéndez, E., and others: Renal Hypertension, Springfield, Ill., Charles C Thomas, Publisher, 1946: (*a*) p. 33; (*b*) p. 36.

2. (*a*) Wilson, C., and Byrom, F. B.: Lancet **1**:136, 1939. (*b*) Friedman, B.; Jarman, J., and Klemperer, P.: Am. J. M. Sc. **202**:20, 1941. (*c*) Patton, H. S.; Page, E. W., and Ogden, E.: Surg., Gynec. & Obst. **76**:493, 1943. (*d*) Ogden, E.; Collings, W. D.; Taylor, A. N., and Tripp, E.: Texas Rep. Biol. & Med. **4**:14, 1946. (*e*) Grollman, A.: Am. J. Physiol. **142**:666, 1944. (*f*) Flasher, J., and Drury, D. R.: Ibid. **158**:438, 1949.

glomerular capillaries that would result in ischemia of this kidney, which would then be a cause of hypertension, or the hypertension and other factors of the experimental procedure might lead to pathological changes which would so reduce the amount of functional tissue in this kidney that the animal would suffer from reduced renal function, and this might lead to hypertension.

The purpose of this paper is to describe the histological observations and perfusion findings in the kidneys of a group of rabbits that had been made hypertensive by the method of unilateral renal ischemia: incomplete ligation of the renal artery,[3] latex encapsulation [4] or wrapping the kidney with cellophane.[4,5] The manipulated kidney was subsequently removed, and the blood pressure of these animals was followed thereafter.[2f] In about one half of the rabbits the blood pressure returned to normal shortly after removal of the manipulated kidney. In the other one half the blood pressure remained high for various periods of time. Some of the latter animals were killed while still hypertensive so that the remaining kidney could be examined.

Some of these kidneys were subjected only to histological or perfusion studies, but most of them were first subjected to perfusion and then to histological study. Because interstitial nephritis was seen in many of the kidneys of the experimental animals, further histological and bacteriologic studies were made in control groups.

METHODS

Blood Pressure.—This was determined without anesthesia by one or both of two methods, a direct [4] and an indirect.[6] Our data concerning the use of both of these blood pressure methods, including our criteria for arterial hypertension, were presented in previous papers (Flasher and Drury [2f]; Flasher, Drury and Sobin [4]).

Histological Examination.—The kidneys were cut lengthwise in the midfrontal plane and put in 4 per cent formaldehyde solution. Blocks of the kidney were embedded in paraffin, cut at 7 microns and stained with hematoxylin and eosin. In addition, sudan III for fat and Mallory's aniline blue for connective tissue were used.

Perfusion.—A solution of modified gelatin (5 per cent W/V) in isotonic sodium chloride solution (Baxter [7]) was used as the perfusion fluid. The animals were anesthetized with ether after receiving 0.2 cc. of 1 per cent solution of atropine sulfate subcutaneously. Ten milligrams (1,000 units) of heparin sodium in isotonic

3. Drury, D. R.: Proc. Soc. Exper. Biol. & Med. **29**:856, 1932; J. Exper. Med. **68**:693, 1938.

4. Flasher, J.; Drury, D. R., and Sobin, S.: Am. J. Physiol. **158**:433, 1949.

5. Page, I. H.: J. A. M. A. **113**:2046, 1939.

6. McGregor, L.: Arch. Path. **5**:630, 1928.

7. This solution was generously supplied by the Baxter Laboratories, Glendale, Calif.

sodium chloride solution (Upjohn) was injected intravenously, the abdomen was opened, and glass cannulas were tied into the renal artery and vein, in that order. The same glass cannulas were used in all perfusions. The perirenal capsule was removed, the ureter was cut, and the kidney was then removed from the body of the animal. The time elapsing from the beginning of the administration of ether to the ligation of the renal artery was usually about 15 minutes; from then to the beginning of the perfusion was about 15 minutes. The kidney was outside the animal's body for only three to five minutes before the perfusion was started. A static perfusion pressure of 150 cm. of perfusion fluid was used. The venous outflow was noted as cubic centimeters per minute (cc./min.) (at least two readings) for each kidney. The average of the readings obtained (the readings usually differed by only 2 to 10 per cent) were then adjusted to cubic centimeters per minute per pound of rabbit (cc./min./lb.). We did not adjust the rate of

TABLE 1.—*Time Intervals of Experiments*

Rabbit	Days from Renovascular Manipulation to Removal of Manipulated ("Ischemic") Kidney	Days from Onset of Hypertension to Removal of Manipulated Kidney	Days from Removal of Manipulated Kidney to Perfusion of the Unmanipulated Kidney (While Rabbit Was Still Hypertensive)
89	149	76-80	113
92	149	76-147	110
170	75	44-59	11
174	249	214-228	6
177	50	5-14	5
181	165	136-148	7
196	138	111-128	6
204	90	34-57	6
209	93	29-44	6
213	97	22-45	7

outflow to kidney weight because that would have incurred errors due to handling and delay. Weighing the kidneys after the perfusion also was not attempted, since it was found that the kidneys would swell to a variable degree as the perfusion progressed. The perfusion system (with a piece of tubing 3/16 inch in diameter in place of the kidney) had a perfusion rate of 78 cc. per minute (at 150 cm. of fluid); this is just twice the highest rate observed in any of the kidneys to be reported (34 cc. per minute).

RESULTS

Five classes of kidneys were studied. Class 1 consisted of the remaining kidneys (unmanipulated) of animals that had been made hypertensive and whose hypertension had persisted after removal of the manipulated ("ischemic") kidney. Class 2 consisted of the unmanipulated kidneys of animals that had been made hypertensive and whose hypertension had subsided after removal of the manipulated kidney. Class 3 consisted of the remaining kidneys of nonhypertensive rabbits

that had been previously subjected only to unilateral nephrectomy. Class 4 consisted of the kidneys of normal rabbits; some of these rabbits had been subjected to direct ear blood pressure determinations.[4] Class 5 consisted of the manipulated kidneys ("ischemic" from latex encapsulation) of hypertensive animals.

The class we were primarily interested in studying was class 1; the other classes served principally as controls. The kidneys of class 1 came from rabbits that had had one kidney manipulated for 50 to 249 days before this same "ischemic" kidney was removed; hypertension had existed for 5 to 228 days when the "ischemic" kidney was removed. About one week after the ischemic kidney was removed, the other kidney was subjected to the perfusion and histological studies; however, two (of the 10 in this group) were allowed to show their persistence of hypertension for 110 and 113 days before the unmanipulated kidney was studied (table 1).

Histological Study.—A careful histological examination was made of the kidneys in class 1 in a search for any changes which might characterize these unmanipulated kidneys of the animals that showed persistence of hypertension. No such changes were observed. The arterial tree of the hypertensive rabbit could not be differentiated from that of the normal animal (fig. 1). In one of the animals in class 1 there was a suggestion of thickening of the media of the interlobular arteries. These changes appeared to be within the normal range. The intima was free of change, and no suggestion of arteriolar thickening such as is seen in human hypertensive vascular disease was observed. No differences could be noted in the juxtaglomerular apparatus in either the hypertensive or the nonhypertensive animals (fig. 2). In one kidney there was a moderate degree of fatty degeneration of the epithelium of the loops of Henle and of the collecting tubules.

In the study of the kidneys of both normal and hypertensive rabbits it was apparent that interstitial nephritis could occur. This lesion, to our knowledge, has been noted only by Goldblatt,[8] and no description was found in the literature. It is seen predominantly in the cortex but may involve the medulla. The early lesion, evidenced by a collection of polymorphonuclear granulocytes and round cells, was observed occasionally in the papillae, but most often in the cortex. In a few kidneys tiny abscesses had formed. Later the cellular infiltrate might be composed only of lymphocytes and plasmacytes. Then there followed an overgrowth of collagenous connective tissue, producing scars of variable size (figs. 3 and 4), the entire process leading to atrophy and

8. Goldblatt, H.: Personal communication to the authors.

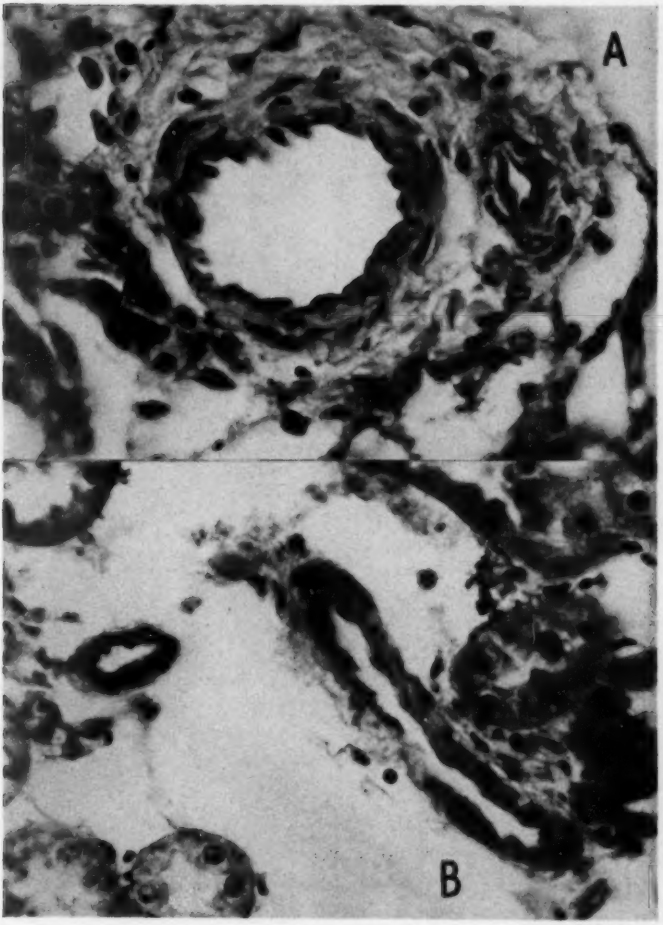

Fig. 1.—*A*, small artery and arteriole in a normal rabbit (class 4-A); × 450. *B*, small artery and arteriole in a hypertensive rabbit (class 1). No changes are seen in the media or the intima; × 450.

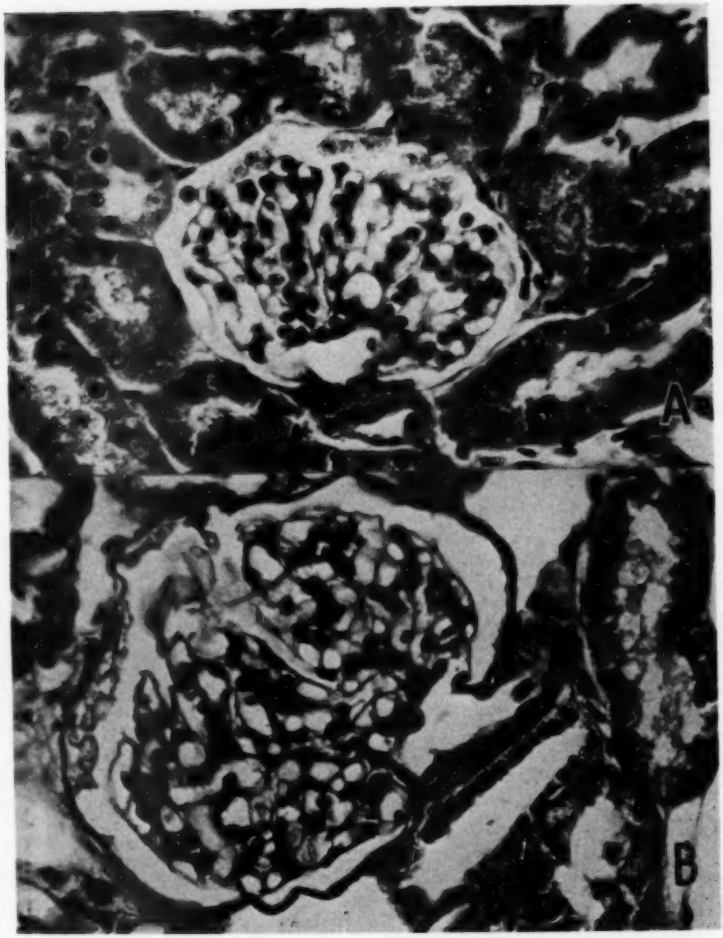

Fig. 2.—*A*, the juxtaglomerular apparatus in a normal rabbit (class 4-A); × 450. *B*, a normal juxtaglomerular apparatus in a hypertensive rabbit (class 1); × 450.

even disappearance of the tubules and eventually of the attached glomerulus, though in many scars the glomeruli seemed remarkably well preserved (fig. 4). The scars were, as a rule, focal in character and involved both the cortex and the medulla.

In normal rabbits which had never been subjected to any laboratory procedure the disease had a low incidence. Minimal or questionable areas of fibrosis and inflammatory infiltrates were the rule, but severe scarring of kidneys did occur (fig. 5). A few gram-positive cocci were noted in an abscess in one of the normal animals. In contrast, those

Fig. 3.—An area of scarring indicating the final stage of healing of interstitial pyelonephritis (class 4-B); × 140.

animals which had undergone any operative or intravenous procedure (such as the direct determination of ear blood pressure) all had a high incidence of cortical lesions (table 2). The distribution of the cortical interstitial lesions in the various classes is shown on a percentage basis in table 2, and the findings in individual rabbits of class 1 are given in table 3. The percentage varied from 12.5 in normal animals to 40 in normal animals that had had only intra-arterial studies and from 66.6 to 75 in normal and hypertensive animals that had had both intra-arterial and intra-abdominal manipulations. Among the animals used in the Friedman test (table 2) one of nine examined (11.1 per cent)

Fig. 4.—*A*, an area of scarring in the cortex of the rabbit whose kidney is shown in figure 5; × 10. *B*, relatively good preservation of glomeruli in the scarred area: × 125.

had interstitial nephritis. Goldblatt [8] studied the kidneys of 180 rabbits and found that 17.2 per cent of the kidneys had an interstitial lesion. These animals had never been subjected to any laboratory procedure. Particularly applicable to the problem is the case of a supposedly normal rabbit (fig. 5) whose kidneys were found diffusely scarred when unilateral nephrectomy was performed. Four blood pressure readings taken over the next five weeks were within the normal range. At

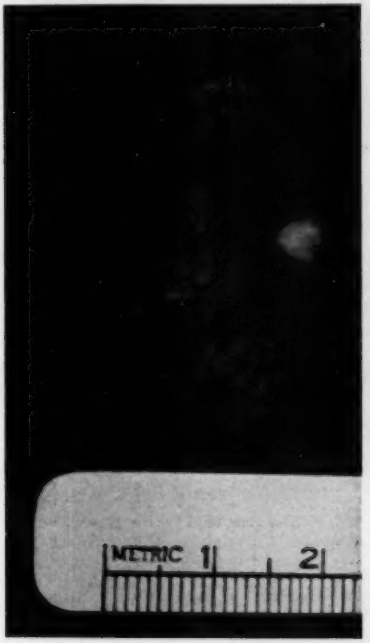

Fig. 5.—Contracted kidney of a rabbit never subjected to any laboratory procedure.

necropsy the opposite kidney was scarred (as observed at the time of laparotomy) and also hypertrophied (compensatory). The heart was normal in size.

We cultured five kidneys from five normal rabbits for bacteria, and Staphylococcus albus was grown from three. Among 18 rabbits given human serum by careful aseptic technic for the Friedman pregnancy test and killed after 72 hours, Staph. albus was grown from the kidneys of seven and coagulase-positive Staphylococcus aureus from three. Nine

of the kidneys containing bacteria were sectioned, and one showed the interstitial lesion (table 2).

Perfusion.—In the 10 rabbits that exhibited persistence of arterial hypertension after removal of the manipulated kidney (class 1), the remaining (unmanipulated) kidney had an average perfusion rate of 2.76 cc. per minute per pound of rabbit. In the 8 animals that did not exhibit persistence of hypertension after removal of the manipulated kidney (class 2), the remaining (unmanipulated) kidney had an average

TABLE 2.—*Incidence of Interstitial Lesions in All Classes of Experimental Rabbits*

	Kidneys Examined	Number with Interstitial Lesions	Percentage with Interstitial Lesions
Class 1	9	6	66.6
Class 2	10	7	70.0
Class 3	8	6	75.0
Class 4			
A*	16	2	12.5
B†	5	2	40.0
C‡	9	1	11.1

* Animals never subjected to any laboratory procedure.
† Animals subjected to intra-arterial punctures only.
‡ Animals subjected to the Friedman test (sterile technic).

TABLE 3.—*Histological Findings in Individual Rabbits of Class 1*

	Scars		Inflammation		
Rabbit	Focal	Gross	Acute	Chronic	Arterial Thickening
89	0	0	0	0	0
92	Occasional	0	0	+	?
174	+	0	0	0	0
181	+	0	0	+−	0
196	+ (few, tiny)	0	0	0	0
198	+	0	0	0	0
204	+ (few)	0	+	0	0
209	0	0	0	0	0
213	0	0	0	0	0

perfusion rate of 2.65 cc. per minute per pound. In the five normal animals that had previously been subjected to unilateral nephrectomy (class 3) the remaining kidney had an average perfusion rate of 2.47 cc. per minute per pound. These differences are probably not significant. In all three of the aforementioned groups of animals the perfused kidney was a hypertrophic kidney. The hypertrophy, of course, was due to the fact that the other kidney had been absent for about three months, or had been "ischemic" (and sometimes atrophic) for periods up to 249 days and absent for about one week or more. In the completely normal group, class 4, the average perfusion rate per kidney (8 animals) was 1.84 cc. per minute per pound.

The perfusion rate in the hypertrophied kidneys (classes 1, 2 and 3) was approximately one and a half that of a single normal kidney (class 4). This corresponds with the observation that after removal of one kidney the remaining kidney hypertrophies to about one and a half times its former size[9] (this takes about one month). Thus, per gram of renal tissue, the perfusion rates were probably similar in all four of the classes just named. When we correct the stated perfusion values for the resistance in the system at the various flow rates, the values and the range obtained are a bit greater, but the conclusions remain the same. Also, there was no apparent correlation between the perfusion rate expressed as cubic centimeters per minute per pound of rabbit and the total weight of the rabbit, so that the slight differences of the average weights in the various groups are probably of no importance.

We also studied some encapsulated ("ischemic") kidneys of rabbits with unilateral renal hypertension (class 5). Most of the kidneys in this group were obviously atrophic; the expected extremely low perfusion rates were noted in the latter, and so we made no attempt to study them in detail. However, in five "ischemic" kidneys that were selected because it was judged that they were approximately normal in size (although they were responsible for initiating the hypertension) the average perfusion rate was 1.81 cc. per minute per pound. This rate is similar to that of the normal rabbits mentioned in a foregoing paragraph (1.84 cc.). Apparently, as judged by our perfusion method, a kidney need not be ischemic at the time it is producing the renal pressor substance. Of course, eventually these encapsulated kidneys do become not only ischemic but finally atrophic, since the fibrocollagenous perinephritis produced by the latex causes progressive constriction of the kidney when a normal kidney is present. Kohlstaedt and Page[10] and others[11] also have presented evidence that a kidney need not be ischemic at the time it is elaborating a pressor or vasconstrictor substance.

The data concerning these five classes of kidneys are presented in table 4.

COMMENT

The interstitial changes observed in the cortex and to a lower degree in the medulla of the kidney in normal and hypertensive rabbits apparently represent an inflammatory lesion which undergoes healing with scar formation. No differences were noted in the disease between

9. Hinman, F.: Arch. Surg. **12**:1105, 1926. Addis, T.: Personal communication to the authors. Addis, T., and Lew, W.: J. Exper. Med. **71**:325, 1940.

10. Kohlstaedt, K. G., and Page, I. H.: J. Exper. Med. **72**:201, 1940.

11. Enger, R.; Linder, F., and Sarre, H.: Ztschr. f. d. ges. exper. Med. **104**:18, 1938. Warthin, T. A., and Thomas, C. B.: Bull. Johns Hopkins Hosp. **72**:203, 1943. Schroeder, H. A., and Steele, J. M.: J. Exper. Med. **72**:707, 1940.

manipulated animals and controls. Bacterial stains on one kidney disclosed that the abscess in the "normal" rabbit contained a few gram-positive cocci. The growth of Staph. albus and Staph. aureus from three of five normal rabbit kidneys and from the kidneys of 10 of 18 rabbits used for the Friedman pregnancy test is strong evidence that a staphylococcus is the etiological agent. Thus it may be that the kidney of the normal rabbit is susceptible to a blood-borne infection leading to interstitial nephritis and that any operation or intra-arterial procedure that introduces organisms into the blood or tissues results in a greatly increased incidence of renal involvement. The direct ear artery blood pressure measurements involved the injection of a small amount of heparin sodium solution that was not handled with sterile precautions. The fact that the cortex was so often the site of greatest change is a

TABLE 4.—*Perfusion Rates Observed in Kidneys from All Classes of Rabbits*

	Kidneys Perfused	Uncorrected Perfusion Rates (Cc./Min.) at a Static Pressure of 114 Mm. Hg.				Average Perfusion Rates Corrected for Resistance to Flow (Cc./Min./Kidney/Lb. of Rabbit)	Weight of Rabbit, Lb.	
		Per Kidney		Per Kidney per Pound of Rabbit				
		Average	Range	Average	Range		Average	Range
Class 1.....	10	20.70	8.75-34.00	2.76	1.91-4.84	3.08	7.56 (3.48 Kg.)	4.50- 9.20 (2.05-4.20 Kg.)
Class 2.....	8	21.21	12.00-33.00	2.65	1.57-4.37	2.93	7.90 (3.70 Kg.)	7.45- 9.25 (3.42-4.22 Kg.)
Class 3.....	5	20.50	14.00-24.00	2.47	1.84-3.82	2.74	8.31 (3.75 Kg.)	6.60-10.75 (3.00-4.87 Kg.)
Class 4.....	8	14.80	8.00-24.00	1.84	1.06-2.66	1.94	8.10 (3.65 Kg.)	4.75-10.25 (2.18-4.63 Kg.)
Class 5.....	5	12.00	8.00-20.00	1.81	1.24-2.44	1.88	6.63 (3.02 Kg.)	4.80- 8.20 (2.20-3.7 Kg.)

further indication that the causative organisms were coming from the blood stream. From a study of table 2 it would seem that no causative relationship exists between the interstitial nephritis and the arterial hypertension. Animals without arterial hypertension had as great an incidence of renal cortical changes as was found in animals that showed persistence of high blood pressure after removal of the "ischemic" kidney.

The histological work of other investigators working with rabbits lends support to our findings. Wilson and Pickering [12] found vascular lesions in various organs in only six of 11 rabbits with what we call bilateral renal hypertension—the usual experimental renal hypertension, in which manipulation of both kidneys is involved. Renal failure was not present in any of these animals. Only one kidney in one of the animals showed these vascular changes; this, however, may only confirm the belief that the kidney is "protected" by the very procedure that makes it "ischemic." Pickering [13] has shown, in rabbits with bilateral renal

12. Wilson, C., and Pickering, G. W.: Clin. Sc. **3**:343, 1938.

13. Pickering, G. W.: Clin. Sc. **5**:229, 1944-45.

hypertension, that removal of the ischemic renal tissue may not return the blood pressure to normal in the few days the animals survive their arenal state; in such animals, he noted that qualitative vascular changes are usually absent.

Friedman, Jarman and Klemperer [2b] showed that the blood pressure of rats with unilateral renal hypertension may not return to normal after removal of the manipulated kidney. In only 20 per cent of the animals that showed this persistence of hypertension could they demonstrate histologically lesions in the remaining (unmanipulated) kidney or body generally; these consisted of hyalinization, inflammation and necrosis of the arterioles and small and medium-sized arteries.

Others present evidence to the contrary in the rat. Patton, Page and Ogden [2c] claimed that they found the arteriolar walls to be thickened, with increased cellularity in all of the unmanipulated kidneys of rats with unilateral renal hypertension. They also found glomerular lesions and interstitial nephritis, as well as large amounts of protein in the urine, that persisted after the ischemic kidney was removed. Schroeder and Newmann [14] found renal arteriolar lesions, including necrosis of the wall, in 47 of 52 rats with unilateral renal hypertension. They found these lesions in the unmanipulated kidney as well as in the "protected" ischemic kidney. This makes the interpretation of the results rather difficult, since it does not correlate with the "protection" of the ischemic kidney observed by others. Byrom and Dodson [15] surmised that the remaining kidney must be the cause of the known persistence of the hypertension after the removal of the ischemic kidney in rats with unilateral renal hypertension. They used rats with bilateral renal hypertension. They first removed one kidney and then made the other kidney ischemic by putting a constricting silver clip on the renal artery. After the animal was hypertensive, they removed the silver clip and noted prompt subsidence of the hypertension. They explained this lack of persistence of the hypertension by the absence of a normal kidney that could have been made ischemic by the hypertension. Also, the previously ischemic kidney was no longer ischemic because the clip had been removed and because while the clip was in place the kidney was "protected" from damage due to the hypertension. In an earlier paper, Byrom and Dodson [16] noted fibrinoid arterial necrosis in the unmanipulated kidney in six of eight rats with unilateral renal hypertension.

Just as was true of our histological studies, our perfusion results did not lend support to the hypothesis that the remaining kidney is in some way involved in the persistence of hypertension after removal of the "ischemic" kidney. Of course, any perfusion method leaves much to be

14. Schroeder, H. A., and Newmann, C. J.: J. Exper. Med. **75**:527, 1942.
15. Byrom, F. B., and Dodson, L. F.: Clin. Sc. **8**:1, 1949.
16. Byrom, F. B., and Dodson, L. F.: J. Path. & Bact. **60**:357, 1948.

desired. There are many other perfusion fluids that could have been used, but all meet with some objections. Most of them produce edema of the tissue as the perfusion proceeds. Cox and Dock [17] claimed that kerosene is the best fluid for postmortem perfusions, since it does not leave the vascular tree, and under the conditions of their experiments it gives renal (human) perfusion rates that are similar to those obtained in vivo under conditions of maximal flow as studied by iodopyracet clearance. They noted that the more physiological perfusion fluids (water, sodium chloride solution, serum or acacia mucilage) give rates that are less than one third of the calculated flow. They kept the kidneys in the ice box prior to perfusion and subjected them to a period of excessive perfusion pressure to "break up rigor." Their method was able to show differences in the perfusability of kidneys from patients with "benign essential hypertension" as compared with those from patients with uremia due to arteriosclerosis, glomerulonephritis or pyelonephritis. The former group had normally perfusable kidneys, while the uremic group showed a great decrease in the rate of perfusion. Their method, however, did not seem advisable for our experiment, since we were trying to discern not only any possible structural narrowing or occlusion of the blood vessels but also any narrowing due to a change in tonus of the vascular musculature. It is certainly true, just as they intimated, that other perfusion methods give rates that are less than the probable rate of blood flow during life.[18] The existence of renal vascular shunts as supported by Trueta and co-workers [19] might vitiate the interpretation of our results. These shunts apparently can divert the blood so that it by-passes most of the glomeruli. If these shunts were called into play by our procedures and were not affected to as great a degree as the smaller vessels of the glomeruli by a pathological process, the kidney might perfuse as though it were a normal kidney. Selkurt [20] has shown that even with only three to five minutes of complete renal arterial occlusion it takes 120 minutes for paraaminohippuric acid clearance to come back to normal.

We do not know what accounts for the persistence of the hypertension after the "ischemic" kidney is removed from a rabbit with unilateral renal hypertension. Reed, Sapirstein, Southard and Ogden [21] produced evidence that the renal pressor mechanism which initiates experimental renal hypertension is later superseded by a neurogenic

17. Cox, A. J., Jr., and Dock, W.: J. Exper. Med. **74**:167, 1941.

18. Forster, R. P., and Maes, J. P.: Am. J. Physiol. **150**:534, 1947. Walker, A. M.; Schmidt, C. F.; Elsom, K. A., and Johnson, C. G.: Ibid. **118**:95, 1937.

19. Trueta, J., and others: Studies of the Renal Circulation, Springfield, Ill., Charles C Thomas, Publisher, 1947.

20. Selkurt, E. E.: Am. J. Physiol. **144**:395, 1945.

21. Reed, R. K.; Sapirstein, L. A.; Southard, F. D., and Ogden, E.: Am. J. Physiol. **141**:707, 1944.

mechanism mediated through the sympathetic nervous system. Others have suggested alternative explanations, just as we [2f] have suggested a change of "set" of a blood pressure regulatory mechanism, to account for the change of mechanism in the course of experimental renal hypertension.

CONCLUSIONS AND SUMMARY

After removal of the "ischemic" kidney producing unilateral renal hypertension in a rabbit the blood pressure remains elevated for some time in about half the animals. The remaining (unmanipulated) kidneys of these animals show no alterations that differ significantly from those found in the kidneys of the control animals when examined histologically in formaldehyde-fixed sections that have been stained with hematoxylin and eosin, sudan III and Mallory's aniline blue. Further, these kidneys when perfused with 5 per cent gelatin in isotonic sodium chloride solution show a perfusion rate, expressed as cubic centimeters per minute per pound of rabbit, that is similar to those of the controls.

Our evidence suggests that the unmanipulated kidney does not play a role—at least structurally—in the persistence of arterial hypertension after removal of the manipulated ("ischemic") kidney in a rabbit with unilateral renal hypertension. The possibility still exists that a functional alteration could be present (as an increase in tonus of the renal vascular musculature) that is not discerned by our perfusion technic.

We also present evidence that a kidney that is elaborating humoral pressor substances need not be "ischemic" as judged by our perfusion method.

The kidney of the rabbit is peculiarly subject to an interstitial nephritis, usually located in the cortex, which tends to heal with the formation of multiple scars. In our experience the disease is not common in animals which have not been subjected to any experimental procedure, but the incidence rose to 60 to 75 per cent in those rabbits subjected to intra-arterial and intra-abdominal procedures. The high incidence of staphylococci noted on culture of control animals' kidneys suggests that they are the commonest offending organisms.

Case Reports

BOECK'S SARCOID OF THE THYROID GLAND

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AND
T. H. GANDY, M.D.
SHREVEPORT, LA.

APPARENTLY any organ or tissue of the body may be affected by Boeck's sarcoid, but involvement of the thyroid gland is extremely rare. Lymphoid tissue is prone to be involved in this disease, and the thyroid contains a variable amount of lymphoid elements which are increased in hyperthyroidism.

In 1938 Spencer and Warren [1] reported the first case in which there was involvement of this organ. Their patient was a 51 year old man in whom generalized Boeck's sarcoid developed and who died. Microscopic examination of the thyroid gland revealed several small lesions of Boeck's sarcoid irregularly scattered throughout the gland; otherwise it was normal.

The case reported by Oldberg [2] in 1943 may be questioned on the basis of his finding a suggestion of necrosis in one tubercle and a single acid-fast bacillus in its center.

Oldberg [2] referred to the clinical observations of Ustvedt and Stallard-Tait. They described similar cases of Boeck's sarcoid with clinical evidence of involvement of the thyroid gland. However, histopathological examinations of these glands were not made.

A review of the literature reveals no other cases. The diagnosis of the illustrated case was made on histopathological structure.

REPORT OF CASE

History.—A 25 year old Negro woman was admitted on February 21, 1949 with a chief complaint of goiter. She first noticed a small mass in the midline of the neck four years previously. This gradually increased in size, and one year prior to admission she began having "smothering spells" at night. These responded to strong solution of iodine U. S. P. but soon recurred, along with nervousness. One month prior to admission she noticed protrusion of the right eye.

She had lost an unspecified amount of weight and complained of frequent headaches, weakness and easy fatigue. Menses had been irregular in that she occasionally missed a period. There were no abnormal respiratory, gastrointestinal or urinary symptoms.

The past history revealed tonsillectomy in 1943 and measles in 1944. There had been no pregnancies or serious illnesses, operations or injuries.

Physical Examination.—Examination revealed a well developed, well nourished woman in no acute distress. There were no lesions of the skin and no enlarged lymph nodes. There was proptosis of the right eye. The pupils were equal and regular and responded to light and accommodation. There was symmetric diffuse enlargement of the thyroid gland, including the isthmus. The trachea deviated slightly to the left. The lungs were clear to percussion and

From the Departments of Pathology, Surgery and Medicine, Shreveport Charity Hospital.

1. Spencer, J., and Warren, S.: Boeck's Sarcoid: Report of Case, with Clinical Diagnosis Confirmed at Autopsy, Arch. Int. Med. **62**:285 (Aug.) 1938.

2. Oldberg, S.: Acta med. Scandinav. **115**:163, 1943.

auscultation. A grade 2 systolic murmur was heard at the cardiac apex and aortic areas. The heart rate was 130 per minute, and the rhythm was regular. The blood pressure was 150/90. The remainder of the physical examination showed essentially normal conditions.

Laboratory Study.—Urinalysis and serologic tests gave negative results. The hemoglobin level was 11.5 Gm. and the white blood cell count was 4,500, with a differential count of 50 polymorphonuclear neutrophils, 35 lymphocytes, 10 monocytes and 5 eosinophils. The serum cholesterol was 115.2 mg. per 100 cc. The basal rate was + 49 per cent.

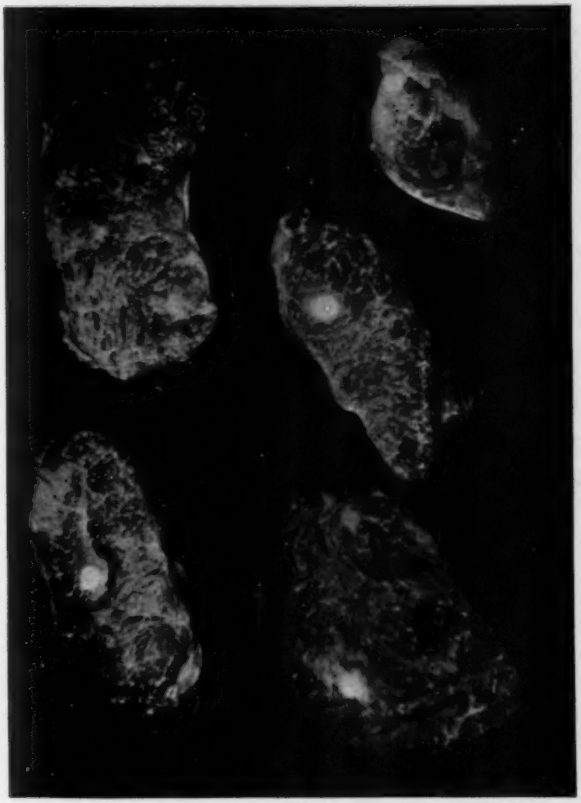

Fig. 1.—Boeck's sarcoid of the thyroid gland characterized by oval-shaped, various-sized circumscribed nodules.

Roentgenograms of the neck revealed soft tissue swelling in the region of the thyroid isthmus. No deviation or compression of the trachea was observed. A roentgenogram of the chest revealed slight prominence and congestion of both hilar regions.

An electrocardiogram showed an inverted T_3 and a diphasic T_1. The heart rate was 120 but otherwise normal.

Course.—The patient was started on propylthiouracil therapy and was given two blood transfusions. She gradually improved, as evidenced by diminishing symptoms and a 10 pound (4.5 Kg.) weight gain in two months. The pulse rate ranged between 70 and 80, and the basal metabolic rate dropped to + 14 per cent. A second electrocardiogram showed only sinus tachycardia. She was given strong solution of iodine U. S. P. for three weeks preoperatively.

On May 9 a bilateral partial thyroidectomy was performed with removal of the isthmus and enlarged pyramidal lobe. She was given 1,000 cc. whole blood during the operation and stood the procedure well.

Gross Examination.—The thyroid gland weighed 40 Gm. and measured 5 by 3.5 by 3 cm. and 5.5 by 5 by 3 cm. The cut surfaces of the lower pole of one of the lateral lobes showed grayish white circumscribed nodules that measured from 2 up to as much as 4 mm. in diameter. There was a similar circumscribed nodule in the middle third of this lobe. Sections of the opposite lobe and the isthmus showed similar nodules scattered through the parenchyma. Occasional nodules were found in the isthmus which were similar to the ones present in the lobes. The parenchyma of the gland was moderately firm and reddish brown (fig. 1).

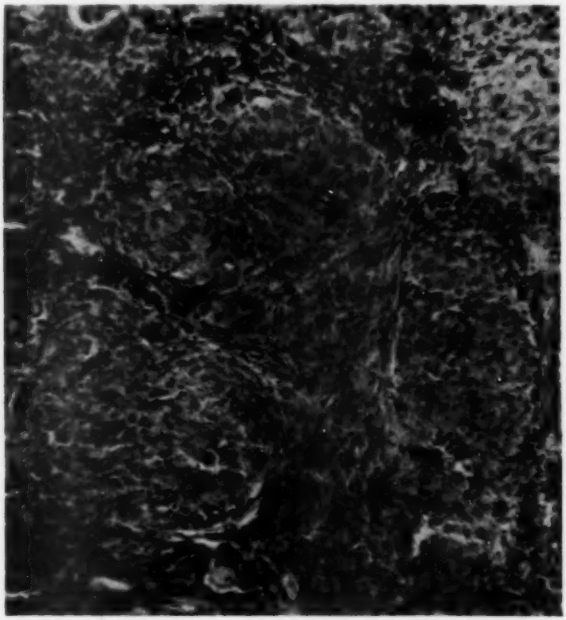

Fig. 2.—Epithelioid tubercle without central necrosis and showing Langhans' giant cells centrally and peripherally.

Microscopic Examination.—Sections showed circumscribed epithelioid tubercles associated with Langhans' giant cells. These cells were located centrally as well as peripherally in the tubercles. No inclusion bodies were found in the giant cells. There was little, if any, evidence of central necrosis. Scattered lymphocytes were found in association with the tubercles. In several foci the acini were small and lined by tall columnar epithelial cells with budding branches that projected into the lumens of the acini. Other areas showed various-sized acini lined by low cuboidal epithelium and distended with colloid (fig. 2).

The microscopic appearances were interpreted as Boeck's sarcoid of the thyroid gland and hyperthyroidism showing involution.

Postoperative Course.—The patient ran an uneventful postoperative course. Her temperature was never above 100.2 F., and her pulse rate remained below 84. The incision healed well, and she was discharged on the fifth postoperative day to be followed as an outpatient.

She was asymptomatic and her tremor and exophthalmos were diminished one month after thyroidectomy and had disappeared two months postoperatively. A roentgenogram of the chest showed no change.

Two months later she was still asymptomatic. The basal metabolic rate was + 30 per cent. The serum cholesterol was 292 mg. and the serum protein 7.8 Gm., with 6.2 Gm. albumin, per 100 cc.; the nonprotein nitrogen was 27.8 mg. Hemoglobin level was 13.5 Gm. The white blood cell count was 4,300. Roentgenologically the chest was essentially unchanged and the hands were normal.

One year's follow-up revealed that the patient was asymptomatic. The blood pressure was 120/80, and the temperature was 98 F.

SUMMARY

A case of Boeck's sarcoid of the thyroid gland associated with hyperthyroidism is presented. A one year follow-up after thyroidectomy revealed that the patient is apparently clinically well. It is believed that the disease process is limited to the thyroid gland in this case.

ACUTE MYELOGENOUS LEUKEMIA WITH GIANT CELL CARCINOMA OF THYROID

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THE COMBINATION of leukemia and carcinoma is not in itself rare. However, a review of the English literature did not reveal a previous report of this exact combination—acute myelogenous leukemia and giant cell carcinoma of the thyroid gland. Because of the extreme malignancy of both diseases and because of the infrequency of the combination, we felt that this case should be recorded.

The first case of carcinoma associated with leukemia was reported in 1878.[1] In an excellent review of the subject, Morrison, Feldman and Samwick [2] collected 21 cases and added two cases of their own. Of the 23 cases reviewed, 15 were of lymphatic leukemia, 7 were of myeloid leukemia and 1 was of the monocytic variety. The carcinomas that occurred in association were of various organs, including stomach, lung, larynx, rectum, kidney, uterus, breast, liver and pancreas. Since this review a case of carcinoma of the larynx and chronic lymphatic leukemia has been reported.[3] With the addition of the present report, the total number of cases of the combination of carcinoma and leukemia is brought to 25.

HISTORY OF CASE

A 54 year old Negro farmer was admitted to the hospital on May 23, 1949. His complaints were referable to a six weeks' illness with sudden onset, characterized by a daily elevation of temperature and a migratory polyarthritis involving knees, left hip, sternoclavicular joints, left ankle and lumbar spine. After the first week of illness, dyspnea and weakness developed, and a cough producing a white sputum which was occasionally streaked with bright red blood. There were night sweats as well. However, no loss of weight was noted.

Physical examination revealed a toxic, anemic man whose temperature was 103 F., pulse rate 120 per minute, respirations 50 per minute and blood pressure 130/?. The head and neck revealed no abnormality. The thyroid was not palpable. The mucous membranes were extremely pale. The chest had many rhonchi, and high-pitched rales were heard throughout both lung fields. However, no evidence of consolidation was elicited. The heart revealed no enlargement, murmur or irregularity. The abdomen was distended and tympanitic. However, no mass or organ was palpable. The knees, the left ankle and the sternoclavicular joints were tender and slightly enlarged. There was a large, palpable lymph node in the right axilla, and smaller nodes were found in the left axilla and in the epitrochlear, cervical and inguinal regions.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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Initial laboratory work revealed 1,770,000 red blood cells per cubic millimeter and 104,000 white blood cells per cubic millimeter, with neutrophils 35 per cent, lymphocytes 16 per cent, myeloblasts 49 per cent and a hematocrit reading of 16 volumes per cent. The standard Kahn test was negative.

A chest roentgenogram on admission revealed moderate generalized cardiac enlargement with prominence of the left ventricle and slight widening of the thoracic aorta. In addition, there were an increase in pulmonary vascularity, indicating congestion and edema, and a nodular type of increased density which was thought to represent bronchopneumonia.

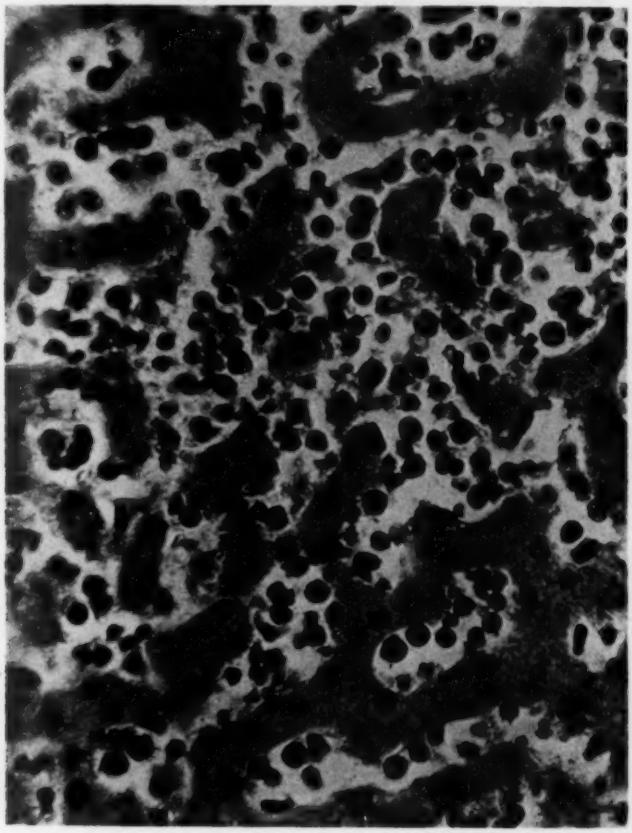

Fig. 1.—Liver showing leukemic infiltration of sinusoids by myeloblasts; × 400.

Clinical Course.—Penicillin therapy was started, and two 500 cc. blood transfusions were given. Rapid digitalization was attempted with combined intravenous and intramuscular administration of digitoxin, and the patient was placed in an oxygen tent. The temperature curve dropped slowly, but by the next day the patient began to fail rapidly, and in spite of all supportive measures a gallop rhythm developed, respiration became more and more difficult and cessation of respiration was followed in a few minutes by cardiac standstill.

Hematological Findings.—Sternal marrow was aspirated four hours post mortem. The total nucleated elements numbered 142,500 per cubic millimeter. No megakaryocytes could be

counted. Fat was absent. The marrow was very hyperplastic, and the erythroid series was almost completely replaced by very immature cells. Smears revealed many myeloblasts, progranulocytes and myelocytes, most of which exhibited the peroxidase reaction. The lymphocytes were of normal appearance.

PATHOLOGICAL OBSERVATIONS

At autopsy the body was that of a well developed man with no obvious loss of weight. The mucous membranes were very pale, but no icterus was present. The

Fig. 2.—Thyroid showing giant cell carcinoma adjacent to a normal thyroid acinus; × 400.

thyroid gland was not palpable. The previously described lymphadenopathy was again noted, but no node over 1.5 cm. in diameter was found. There was 500 cc. of clear yellow fluid in the right pleural cavity and 150 cc. of similar fluid on the left, but no excess fluid was found in the peritoneal or the pericardial cavity. The heart weighed 520 Gm., and its epicardial surface was covered with petechiae. The right and the left lung weighed 1,020 and 950 Gm., respectively, and had many petechiae on their pleural surfaces. They were edematous and had a doughy consistency in their apexes. The spleen weighed 80 Gm. and was grossly normal. The

stomach and jejunum contained numerous mucosal petechiae. The left lobe of the thyroid contained a firm, yellowish white nodule which was well circumscribed, measuring 2 cm. in diameter, and appeared to be confined to the parenchyma of that organ. There was gross evidence of leukemic infiltration in the myocardium, the kidneys, the bone marrow and the lymph nodes. Microscopically, the above-mentioned findings were confirmed, and leukemic infiltration of lungs, liver (fig. 1), spleen, stomach, colon, testis and epididymis was found. The nodule in the thyroid was composed of large, pleomorphic, single-nucleated and multinucleated giant cells with a variable amount of reticulated pink cytoplasm (fig. 2). Mallory's phosphotungstic acid and hematoxylin stain and Gomori's silver stain added no significant information. There was microscopic evidence that this tumor was infiltrating adjacent skeletal muscle. Also a metastatic tumor of similar histologic character appeared in a hilar lymph node.

COMMENT

The occurrence of either acute myelogenous leukemia or giant cell carcinoma of the thyroid, while not rare, is certainly infrequent. According to Wintrobe,[4] about 3,500 people die in the United States annually of leukemia, and of this number approximately 311, or 8.8 per cent, die of acute myeloblastic leukemia.

As an indication of the infrequency of carcinoma of the thyroid, it was found that 6,535 persons were operated on for thyroid disease in one large clinic from 1916 to 1930 and that only 2.86 per cent of these proved to have a cancer of the thyroid gland.[5] Furthermore, only about 11 per cent of those who had carcinoma of the thyroid had the giant cell variety.[6] Therefore, we most certainly consider this particular type of cancer very infrequent. The combination of two such uncommon diseases in the same patient is indeed rare.

This particular case presents many unusual features. Acute leukemia is uncommon in Negro men over 50 years of age.[7] Only two cases occurred among 13 cases of leukemia in this age group studied at Charity Hospital, New Orleans. The duration of the illness was short (six weeks), especially if one considers that the history of joint symptoms may not have been associated with the patient's blood disease. The nature of the onset with swelling of the knees and fever is also an unusual one. Another unusual feature is the small spleen. The average weight of the spleen in seven cases of acute leukemia was 434 Gm., and in no case did the spleen weigh less than 100 Gm.[7]

The incidental finding at autopsy of a rather uncommon cancer of the thyroid gland in a patient dying of acute myelogenous leukemia is perhaps most significant. In the first place, carcinoma of the thyroid is more commonly a disease of women, and this particular cell type is not common. The small size of the primary tumor in the thyroid and its failure to produce symptoms or physical changes, along with the fact that it had invaded skeletal muscle and metastasized to a hilar lymph node, attest the rapid spread and early metastasis for which the disease is noted.

SUMMARY AND CONCLUSIONS

A giant cell carcinoma of the thyroid gland of a patient dying of acute myelogenous leukemia is presented.

Twenty-four previously reported cases of leukemia associated with carcinoma are noted.

The rarity of the combination of two such uncommon diseases in the same patient is stressed.

To our knowledge this is the first reported case of the association of carcinoma of the thyroid and leukemia.

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INTRAMURAL ABSCESS OF STOMACH (PNEUMOCOCCUS TYPE VIII)

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AN ABSCESS of the stomach is a rare lesion, usually discovered unexpectedly at operation or necropsy. Despite its rarity, cases have been described in the earliest medical literature. Galen described the first case on record,[1] but the earliest relatively complete accounts appeared in the late seventeenth century (Varandaeus, Borel, Sand, Bovet).[2] All these cases were instances of the circumscribed form of phlegmonous gastritis and were described before the diffuse form had been recognized. Sundberg,[3] Novak[2] and Gerster[1] have written complete reviews of phlegmonous gastritis. Two forms of the disease are recognized: the diffuse and the circumscribed. Of the former, much has been written, especially in the foreign literature. Of the latter, up to 1919 about 25 acceptable cases had been reported (Novak).[3] Rankin and Miller,[4] in 1931, stated that "abscesses constitute about 12 per cent of all purulent inflammatory lesions of the stomach." Since 1931 we have found reports of only 3 cases[5] of the circumscribed form; among these was that of Rankin and Miller.[4]

The purpose of this report is to present a case of an intramural abscess of the stomach, presumably caused by Pneumococcus type VIII.

HISTORY OF CASE

The patient was a 54 year old white man, a bartender, who was admitted to Grasslands Hospital for the second time on Dec. 6, 1949 with chief complaints of vomiting and constant dull pain of three weeks' duration in the right upper quadrant of the abdomen.

He was first hospitalized in 1935 at another institution, where a diagnosis of pyelitis was made. In November 1937 he fractured his eleventh rib; later the same year he was admitted for the first time to the Grasslands Hospital Psychiatric Institute for four days because of acute alcoholism. In 1939 he fractured the left sixth and seventh ribs and was again hospitalized for a four day period.

The patient's first pertinent hospital admission occurred in March 1943 (at another institution). At that time he had a two month history of chills, sweats, constipation, vomiting and pain in the right upper quadrant of the abdomen. This pain was intermittent and was occasionally relieved by enemas. These episodes were provoked by drinking bouts. He ate poorly, sometimes neglecting to eat over a three day period. At times he noticed that his urine became scanty and dark, "almost like blood." He stated that his symptoms decreased

From the Division of Pathology, Grasslands Hospital, and the Department of Laboratories and Research of Westchester County.

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when his urine returned to a "normal" color. A diagnosis of acute cholecystitis and cholelithiasis was made. A laparotomy was performed, and "the lesser sac was drained of 500 cc. of straw-colored fluid"; the gallbladder and the appendix were grossly normal; the pancreas seemed to be edematous, large and hard. A postoperative diagnosis of acute pancreatitis was made.

During a one year period following this operation he had intermittent attacks of vomiting, poor appetite, anemia, chills and sweats and lost 50 pounds (22.5 Kg.). The pain in the right upper quadrant gradually returned, and two months after his first operation he became jaundiced "for a few weeks."

He was admitted again to the same hospital in 1944 with similar symptoms. His urine was darker for a few days prior to this admission. On physical examination the liver was palpated 4 cm. below the right costal margin. A roentgenogram of the chest revealed no abnormality. A gastrointestinal series was interpreted as showing a filling defect in the region of the pylorus; the impression was that an extragastric or a submucosal mass existed. There was also narrowing of the second portion of the duodenum.

At operation a questionable mass in the region of the head of the pancreas was noted; it was "hard and nodular." The gallbladder wall was thickened and the common duct dilated. The gallbladder was "filled with inspissated bile, and adhesions were noted crossing the duodenum." The appendix was removed and showed "chronic inflammation." A cholecystotomy was also done "to relieve the pancreas of back pressure and irritation of bile back-up." Biopsy of the liver revealed "chronic cholangitis, probably the result of back pressure"; a lymph node from near the head of the pancreas was diagnosed as "sinus catarrh." Postoperatively the patient was given one blood transfusion. He was discharged in good health one month and a half after admission.

He was readmitted one month later for a 14 day period because of a sinus in the right upper quadrant of the abdomen, which was draining bile. The sinus closed spontaneously.

He was apparently well until April 1947, when he was readmitted to the hospital with a diagnosis of chronic cholecystitis and possible pancreatitis. His symptoms were of three weeks' duration and consisted of severe nausea and vomiting, which occurred one half to one hour after intake of food and were associated with right upper quadrant pain. For one week prior to admission only fluids were tolerated. There was a 30 pound (13.5 Kg.) loss of weight and constipation but no jaundice. Urinalysis revealed albumin (1 +), glucose (2 +), a specific gravity of 1.010, a few red cells, numerous bacteria and 20 to 30 white cells in clumps per high power field. The red blood cell count was 4,940,000, and the hemoglobin content was 100 per cent; the white blood cell count was 13,500, with 87 per cent polymorphonuclear granulocytes and 13 per cent lymphocytes. The patient was discharged improved after an eight day stay in the hospital without specific therapy.

Present Admission (Dec. 6, 1949).—The patient was relatively well until two weeks prior to this admission to Grasslands Hospital, when, after an alcoholic bout, frequent vomiting recurred, with dull pain in the right upper quadrant of the abdomen The vomiting occurred shortly after the ingestion of any food or fluid. There were mild chilly sensations and a 30 pound loss of weight. A bland diet and mild sedation helped only temporarily.

Physical Examination.—The patient was a well developed but poorly nourished white man, appearing acutely and chronically ill. His temperature was 98 F., pulse rate 96, respirations 16 and blood pressure 135/80. Except for evidence of dehydration and moderate tenderness over the area of the two old right upper quadrant scars the findings were noncontributory.

Laboratory Data.—The red blood cell count was 5,990,000; the hemoglobin content was 15 Gm. (Haden-Hauser); the white cell count was 25,550, with 76 per cent polymorphonuclear granulocytes, 6 per cent metamyelocytes, 1 per cent eosinophilic granulocytes and 17 per cent lymphocytes; the erythrocyte sedimentation rate was 7 mm. in one hour (Westergren). The urine showed a 3 + reaction for albumin, a specific gravity of 1.015, no glucose, an acid reaction; the sediment contained a few white blood cells and many hyaline casts. Blood nonprotein nitrogen was 120 mg., blood creatinine 4.8 mg., blood sugar 130 mg. and blood chlorides 380 mg. per 100 cc. The carbon dioxide-combining power was 102 volumes per cent. Pneumococcus type XI was cultured from the nasopharynx.

Hospital Course.—The patient continued to vomit ingested food and fluids. On the second hospital day a barium sulfate enema failed to show any lesion. A gastrointestinal series showed a large gastric residue at the end of six hours and a dilated stomach. The duodenal bulb never filled; peristalsis was active. These findings suggested an "obstruction of the pylorus due either to a chronic ulcer or to a cancer." Free gastric hydrochloric acid was absent after histamine stimulation.

During his hospitalization the patient's temperature indicated an intermittent low grade fever, with occasional spikes to 100.8 F. Chemical studies of his blood indicated a return to normal values prior to operation. After he had been prepared with a high protein, low residue diet, a laparotomy was carried out one month after admission.

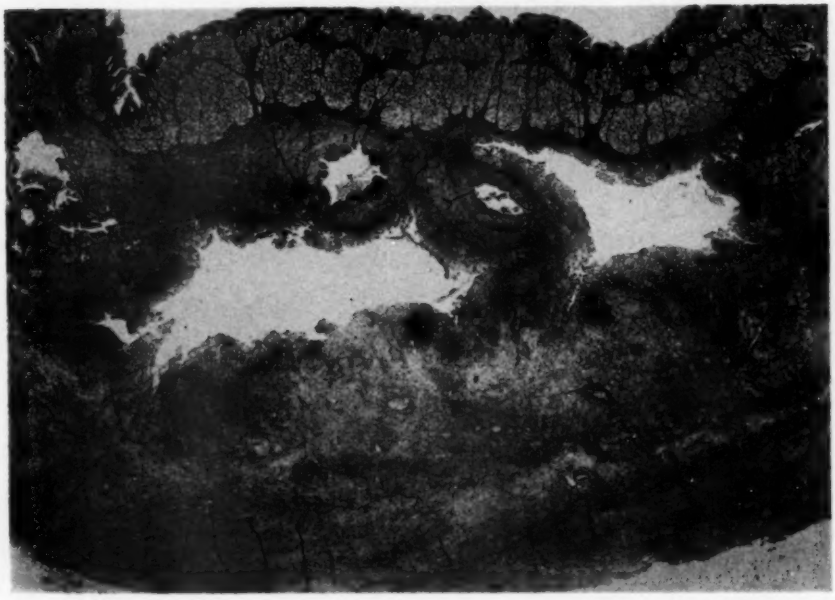

Fig. 1.—Photomicrograph showing the stomach wall with the intramural loculated abscess (hematoxylin and eosin; × 9). The dilated duct shown in figure 3 can be seen between the abscess and the mucosa; other ducts are seen to the left of the abscess. The pyloric ring begins at the extreme left of the field.

The omentum was adherent to the anterior surface of the gastric wall. A partial gastrectomy was performed, with removal of the distal half of the stomach and 1 inch (2.5 cm.) of the duodenum. During the operative procedure 1,500 cc. of blood was transfused.

The patient's postoperative course was smooth. He was discharged on Jan. 28, 1950, approximately seven weeks after admission, symptom free.

PATHOLOGICAL OBSERVATIONS

Gross Findings.—The specimen consisted of the distal half of the stomach and the proximal 2.5 cm. of the first portion of the duodenum. On the lesser curvature of the pyloric portion of the stomach was a soft, fluctuant mass measuring 5 cm. in its greatest diameter. The mucosa over this mass was intact; the serosa was slightly thickened. On section there was a multiloculated abscess measuring 4 cm. in its greatest diameter in the submucosa, containing approximately 5 cc. of creamy,

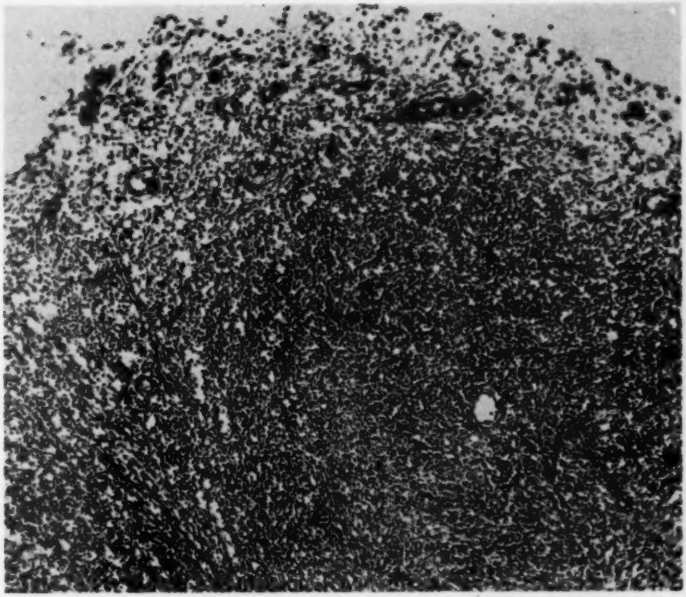

Fig. 2.—Photomicrograph showing abscess wall (hematoxylin and eosin; × 100).

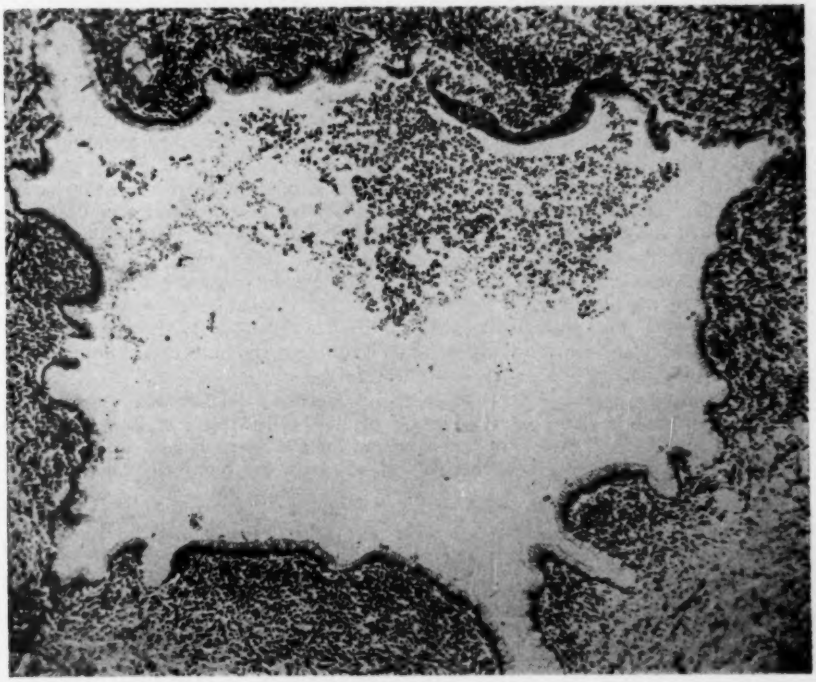

Fig. 3.—Photomicrograph showing a dilated duct of Brunner's gland containing purulent material adjacent to the abscess (hematoxylin and eosin; × 100).

yellowish, purulent material. (Culture of this material yielded Pneumococcus [type VIII] in pure culture. A roentgenogram of the specimen showed no radiopaque foreign bodies.)

Histologic Findings.—The abscess was confined to the submucosa (fig. 1). It contained purulent material consisting mostly of necrotic polymorphonuclear granulocytes; the wall was composed of dense fibrous tissue, infiltrated with polymorphonuclear granulocytes, eosinophilic granulocytes and mononuclear cells (fig. 2). The adjacent tissue showed fibrosis and small collections of mononuclear cells and eosinophilic granulocytes; there were also a few lymphoid follicles. Dilated ectopic ducts of Brunner's glands, containing purulent material, were present in the abscess capsule near the pyloric ring (fig. 3). These ducts were lined by cuboidal epithelium with basal nuclei and clear eosinophilic cytoplasm. The mucosa and the muscularis were intact. The serosa was slightly thickened by fibrous tissue and contained several small focal collections of mononuclear cells with occasional multinucleated giant cells. A few doubly refractive crystals were found in these lesions.

Sections of the surrounding stomach and duodenum revealed no inflammatory reaction.

COMMENT

Numerous factors have been considered in the etiology of gastric abscess. Among these are trauma,[6] carcinoma,[7] foreign body,[8] septicemia [9] and alcoholism.[5a] Submucosal eosinophilic granuloma has recently been reported, probably due to an allergic factor.[10] Gerster [1] stated that in many cases the abscess is due to postoperative complication.

The great majority of gastric abscesses are probably the circumscribed form of phlegmonous gastritis. It is now generally considered that phlegmonous gastritis is a manifestation or a complication of septicemia.[1] The commonest causative organism is the Streptococcus (90 per cent),[9] although the Staphylococcus, the Pneumococcus, Bacillus subtilis and Escherichia coli have also been cultured.[1] The finding of the pneumococcus in this case is unusual.

Most likely, in this case the abscess is a form of circumscribed phlegmonous gastritis. Alcoholism, which has been implicated as a contributory factor in the causation of this lesion,[5a] was present in this case. The chills and the fever may have been due to bacteremia. Unfortunately, blood culture studies were not performed. There is a possibility that the abscess was a postoperative complication, as suggested by Gerster.[1] In the absence of a more specific history the exact cause remains obscure.

Such abscesses are almost always confined to the submucosa,[5a] although some have involved the muscularis. Suppuration of the regional lymph nodes has also been reported.[4] The abscess is usually situated on the lesser curvature of the stomach. This case conforms to the usual pattern in the submucosal and lesser curvature location.

The presence of ectopic ducts leads one to speculate whether this lesion is an abscess of Brunner's glands or whether the infection gained entrance through these ducts. Popoff,[11] in a review of the pathology of the stomach, and Robertson,[12] who discussed the pathology of Brunner's glands, have not described or considered

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12. Robertson, H. E.: Pathology of Brunner's Glands, Arch. Path. **31**:112-130 (Jan.) 1941.

the possibility of such a lesion. It is probable that the ducts of the gland are merely secondarily involved in the abscess wall and fixed there during exacerbations and remissions of the inflammatory reaction.

Cures by partial gastrectomy have been reported, the first in 1918.[13] Gerster collected eight cases in which cure was effected by surgery up to 1927.[1] Until the advent of chemotherapy the operative mortality was 90 per cent.[4]

The most frequent preoperative diagnoses have been gastric ulcer or cholecystitis; to date the correct diagnosis has not been made preoperatively.

It seems likely that given a history of intermittent pyloric obstruction, chills and fever, and roentgenologic evidence of a pyloric obstruction due to a nonulcerating lesion, the diagnosis of intramural abscess of the stomach wall could be entertained.

SUMMARY

A case of an intramural abscess of the stomach (circumscribed phlegmonous gastritis) due to Pneumococcus type VIII is reported.

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ADENOCARCINOMA OF THE TESTIS OCCURRING IN INFANTS

Report of Two Cases

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ADENOCARCINOMA of the testis, of an unusual morphological appearance, occurred in infants 14 and 22 months of age.

REPORT OF CASES

CASE 1.—L. B. S., a boy 22 months of age, was observed, in February 1947, to have a firm mass in the scrotum on the left side. This was about the size of a walnut, was not tender and did not increase in size. On March 25, 1947, the child was brought to the Saskatchewan Cancer Clinic. There the mass was estimated to be about 3 cm. in diameter and appeared to consist of a smooth, rounded enlargement of the testicle. Nothing else abnormal was noted on physical examination. An Aschheim-Zondek test was negative. On March 29, a simple left orchidectomy was done with section of the spermatic cord at the internal inguinal ring. Roentgen therapy was given after the operation. The operative incision healed well, and the child returned home. Reexaminations were done at intervals of a few months. On Oct. 28, 1949 the boy appeared healthy. Physical examination and radiological examination of chest and abdomen revealed no abnormality.

Pathological Report.—The specimen consisted of the testis, the epididymis and an attached portion of spermatic cord. On dissection the spermatic cord and the epididymis revealed nothing of note. The tunica albuginea was smooth, glistening, grayish and intact. Cross section of the testes, which was slightly enlarged and very firm, revealed the normal testicular tissue to be completely replaced by pale, whitish yellow, glistening, moist tissue.

Microscopic Description.—Paraffin sections were stained with hematoxylin and eosin, with Verhoeff's elastic tissue stain and by Van Gieson's method.

The neoplasm presented a pattern of irregularly branching, intercommunicating acinous spaces of varying size and shape, set in a loose fibrous stroma (fig. 1). The acini contained loose shreds of pale eosinophilic material. They were lined by cells which varied somewhat in appearance, being for the most part columnar with basophilic, finely vesicular oval nuclei and moderately abundant pale eosinophilic cytoplasm. Many cells contained oval cytoplasmic vacuoles of varying size, generally situated far from the luminal border of the cell, although many vacuoles were situated next to the lumen. Some of the vacuoles were very large and distended the cell cytoplasm to a thin peripheral rim, the nucleus being displaced

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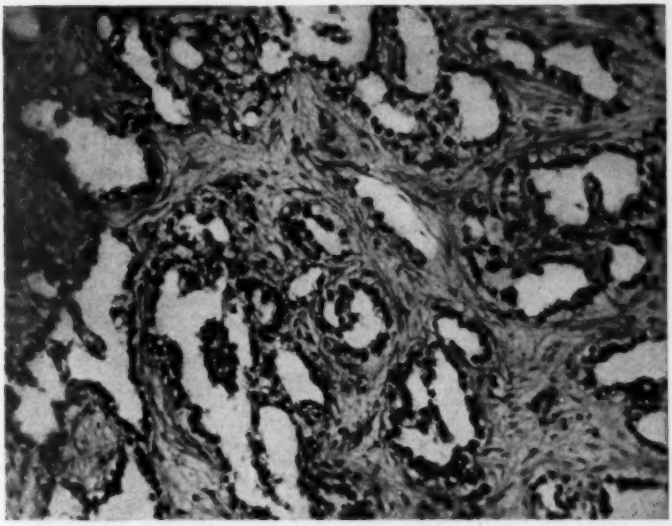

Fig. 1 (case 1).—The tumor cells form large irregular branching acini set in an abundant loose fibrous stroma. × 200.

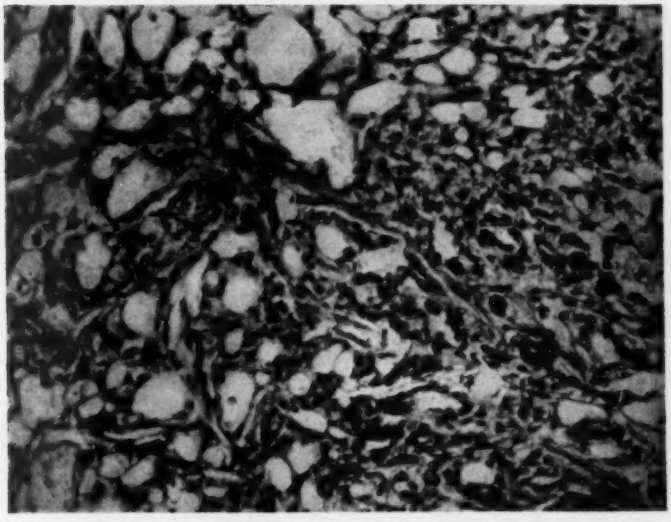

Fig. 2 (case 1).—The tumor cells form small acini and are also arranged in loose strands and masses. The stroma is unconspicuous. × 200.

to one side. The cells lining the acini were arranged in single or double layers or in irregular, jumbled strands, several cells in thickness. In some situations the cells were thinned and flattened, their central nuclei representing their greatest thickness. Some acini showed a transition between columnar cells and flattened cells.

Although the tumor cells for the most part lined acinous spaces, some were disposed in loosely arranged strands (fig. 2). Marked cytoplasmic vacuolation gave such strands a loose, irregular meshlike pattern. In some areas there was coalescence of large vacuoles in adjoining cells (fig. 3). Strands of cells merged indefinitely into fields showing a clearcut acinous pattern.

The stroma was composed of loose strands of collagenous connective tissue. This varied in quantity. In many areas broad bands of connective tissue coursed

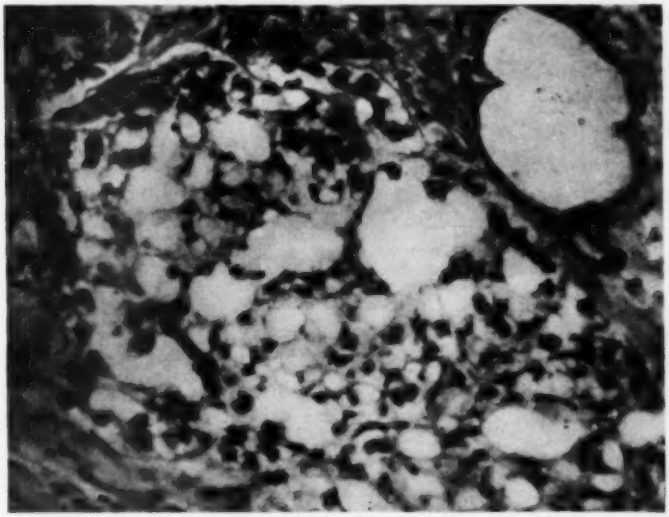

Fig. 3 (case 1).—A higher magnification of a more solid portion of the tumor, to show the marked vacuolation of tumor cells, with coalescence of vacuoles to form acinous spaces. × 400.

between the acini. Elsewhere tumor cells predominated, generally in meshwork formation or as small acini.

For the most part the neoplasm was confined by the tunica albuginea. In some situations a thin rim of compressed spermatic tubules was present between the margin of the neoplasm and the tunica albuginea. No definite capsule was interposed between tumor tissue and spermatic tubules. Some tubules, as a matter of fact, were islanded by tumor tissue, which had apparently infiltrated between them.

Diagnosis.—Adenocarcinoma of the testis.

CASE 2.—J. S., a boy 10 months of age, was noted to have an enlargement of the scrotum on the right side, in February 1947. His mother stated that this

had increased in size. He was admitted to hospital on June 10, 1947, at which time the scrotum was reddened and the testicle enlarged, hard, smooth and non-tender. The results of the physical examination were otherwise negative. On June 14, 1948 simple orchidectomy was done. On receipt of the pathological report the patient was sent to the Saskatchewan Cancer Clinic, where roentgen therapy was given. The incision healed well, and the child returned home. Repeated follow-up examinations revealed that the child was well. The last reported examination was on Oct. 17, 1949, at which time the results of physical examination and radiological examination of the chest were negative.

Pathological Report.—The specimen consisted of testis, epididymis and a portion of the spermatic cord. The epididymis and the cord appeared normal. The

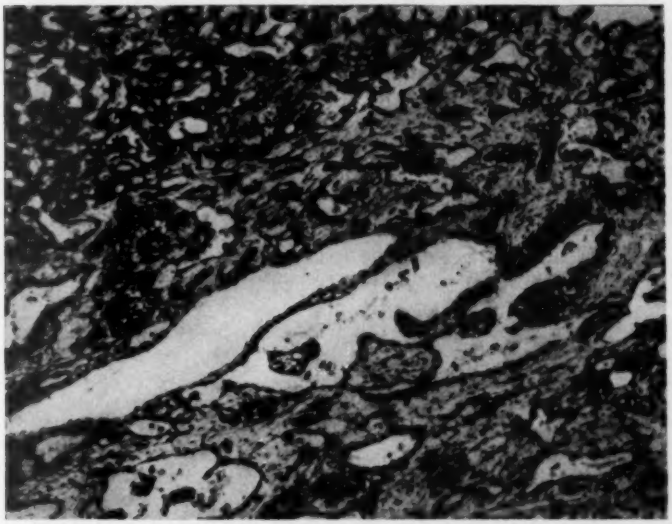

Fig. 4 (case 2).—Large, irregular, branching tumor acini merge into a more cellular area where the acinous spaces are smaller. × 150.

testis was firm in consistency and was slightly enlarged. The tunica albuginea was intact, smooth and glistening. Cross section showed the normal parenchyma to be replaced by firm, glistening, moist, whitish yellow tissue.

Microscopic Description.—Paraffin sections were stained with hematoxylin and eosin, with Verhoeff's stain for elastic tissue and by Van Gieson's method.

The neoplasm was, in some areas, extremely cellular, being composed of masses of small, narrow, irregular, branching acini, lined by columnar cells with hyperchromatic vesicular nuclei. These lining cells, which were often several layers in thickness, showed a number of small vacuoles. Many of them, over segments of the walls of acini, were flattened (fig. 4). Short papillary projections, with expanded ends, seemed to hang into some icini (fig. 5). Many acinous spaces contained desquamated rounded swollen lining cells and also pale amorphous debris.

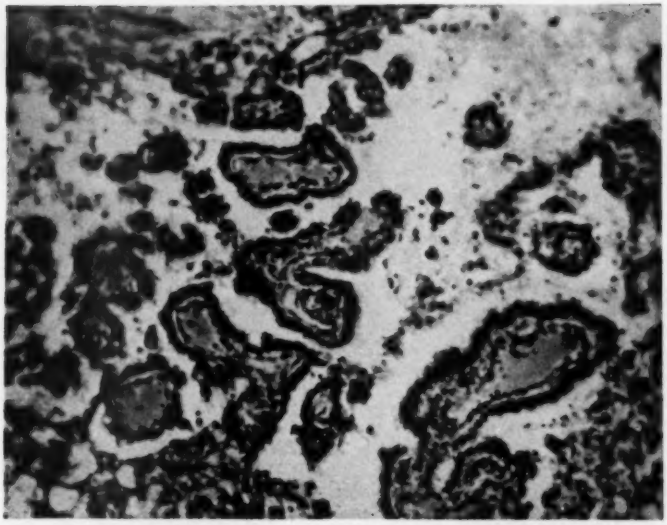

Fig. 5. (case 2).—Degeneration of tumor tissue has occurred, leaving viable tumor cells disposed about engorged stromal blood vessels. × 200.

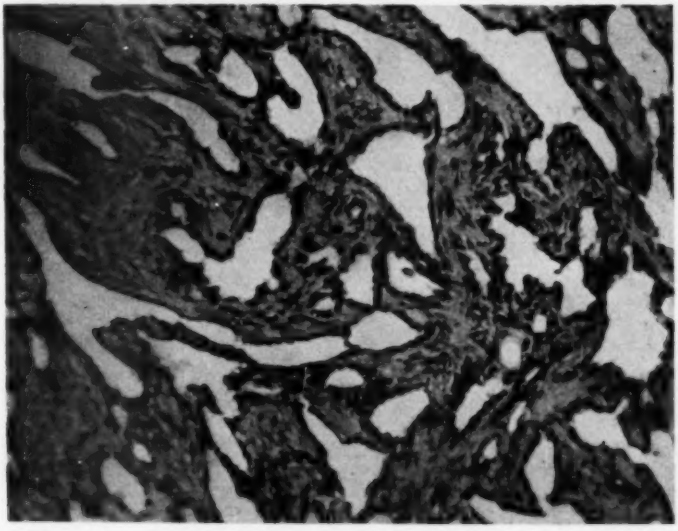

Fig. 6. (case 2).—This photomicrograph is from uninvolved rete testis. The basic pattern here resembles that seen in some areas of both tumors. × 150.

In areas such as these the stroma was scanty. Engorged capillary blood vessels were conspicuous.

Over wide areas the tumor cells lay in a loose mesh, made up of abundantly vacuolated cells, many of which seemed to be fusing in small syncytial groups. In some such groups coalescence of vacuoles formed acinous-like spaces lined by flattened nuclei, sheathed in cytoplasmic wisps.

Elsewhere again the pattern was very similar to the predominant pattern in the tumor in case 1—loose, wide branching acini, lined by low columnar cells, sometimes vacuolated, and by flattened cells. These acini were set in an abundant, loose, somewhat myxomatous stroma. Here and there were zones in which stromal vascular spaces were markedly congested. One vessel contained a recent thrombus.

The neoplasm was bounded by the tunica albuginea, which was thinned and stretched. No spermatic tubules remained visible. Sections from the rete testis showed its tubules to be widened, but it was not invaded by the neoplasm (fig. 6).

Diagnosis.—Adenocarcinoma of the testis.

COMMENT

While there is no uniformity in nomenclature, there is general agreement that the fundamental patterns encountered in teratoid testicular neoplasms are three in number, any two or all three of which may overlap in an individual tumor. Moon and Hullinghurst,[1] in a recent review of 125 tumors of the testis, distinguished these three patterns under the terms "seminoma," "carcinoma" and "teratoma," including under the second term the types which have been called "embryonal carcinoma" and "chorio-epithelioma." The two tumors here described were morphologically quite distinct from seminoma and teratoma. While they were similar to tumors of the carcinoma pattern, they did not resemble the embryonal carcinoma of adults. The large branching acini set in an abundant fibrous stroma, lined by cells varying from flattened to columnar in type and frequently showing much cytoplasmic vacuolation, were unlike those of the usual embryonal carcinoma.

Morphologically these neoplasms bore a certain resemblance to that group of relatively rare genital tract tumors which has been described in the recent medical literature under a variety of names, the most suitable one of which seems to be that of Golden and Ash,[2] namely, "adenomatoid tumor." These have been reported as occurring in the epididymis, in the testicular tunics and on the serosal surface and in the walls of the uterine tubes. Similar but more diffuse and less clearly neoplastic formations have been described in myoma of the uterus, and in the ovary, by Morehead.[3] Although the histological appearance varies somewhat, the unifying feature is the presence of large and small glandlike spaces lined by cells which have been variously interpreted as being epithelial,[4]

1. Moon, H. D., and Hullinghurst, R. L.: Am. J. Path. **24**:1067-1075, 1948.

2. Golden, A., and Ash, J. E.: Am. J. Path. **21**:63-79, 1945.

3. Morehead, R. P.: Arch. Path. **42**:56-63, 1946.

4. Gordon-Taylor, G., and Ommaney-Davis, C.: Brit. J. Surg. **29**:260-262, 1941-1942.

mesothelial [5] and endothelial [6] in origin. The cells are often vacuolated. The neoplasms are small, circumscribed, and are thought to be clinically benign. Despite marked similarities in histological appearance, notably the variation in thickness of the acinous cells and their frequent vacuolation, the tumors reported here could not be classified with the adenomatoid genital tract tumors. Such tumors are not known to occur within the testis, and Ash,[7] who examined sections in these cases, stated that their structure was in general more organoid in nature than that of the adenomatoid tumors.

Vacuolation being a prominent feature of the tumor cells in these two cases, the possibility of an origin from Sertoli cells was considered, since Scully and Parham [8] have reported a case of multicystic adenocarcinoma in a 60 year old man, to which they tentatively assigned a Sertoli cell origin, partly on the basis of vacuolation of tumor cells. This, they stated, recalled the appearance of the Sertoli cells in atrophic testicular tubules and in the Sertoli cell carcinoma of dogs. However, they described a colloid material which was present in the cystic spaces and lining cells and which was absent in the tumors here reported. Further, the microscopic pattern in our cases was unlike that described and illustrated in the case of Scully and Parham. It is to be noted that the authors grouped their case with those reported by Stevens and Ewing [9] and by Stofer,[10] in which multicystic testicular tumors were believed to have arisen from adult seminiferous epithelium. It is also of interest that in Stofer's case areas were described in which the tumor pattern somewhat resembled rete testis.

In our cases the microscopic appearance suggested an origin from rete testis, since some fields showed elongated branching acini, which, it was not difficult to imagine, might represent a transition from rete tubules. While tumors of rete origin are rare, Feek and Hunter [11] reported a rete carcinoma in a man aged 59, and Scully and Parham [8] described a similar tumor in a 48 year old patient.

In the former case the growth was mainly outside the testis and in the sac surrounding it, while in the latter the tumor radiated from the hilus into the testicular parenchyma. In our first case no recognizable rete tissue was seen, but in case 2 the rete tubules, although dilated, seemed to be quite distinct from abutting neoplastic formations. These findings, as well as the fact that the tumors were situated within the testis, led us to question the possibility that they took origin from adult rete structures. However, the extreme youth of the patients suggests the likelihood of a dysontogenetic origin for them, and since they were intratesticular in location, an origin from elements of the primitive testis cords or from the rete blastema must be considered. Their histologic appearance is in favor of the latter source.

5. Masson, P.; Riopelle, J. L., and Simard, L. C.: Rev. canad. de biol. **1**:720-741, 1942.

6. Halpert, B.: J. Urol. **48**:536-538, 1941.

7. Ash, J. E.: Personal communication to the authors.

8. Scully, R. E., and Parham, A. R.: Arch. Path. **46**:229-242, 1948.

9. Stevens, A. R., and Ewing, J.: Ann. Surg. **88**:1074-1078, 1928.

10. Stofer, B. E.: Arch. Path. **40**:68-71, 1945.

11. Feek, J. D., and Hunter, W. C.: Arch. Path., **40**:399-402, 1945.

We are of the opinion that both these tumors, although morphologically well differentiated, were of low grade malignancy. The fact that there has been no recurrence in either case after orchidectomy and roentgen therapy does not invalidate this thesis. As is well known, cancerous neoplasms of the testis frequently are successfully treated by such means.

SUMMARY

Two tumors diagnosed as adenocarcinoma of the testis, occurring in children of 14 and 22 months, are reported. We believe these neoplasms to have been of a morphologically distinctive type, and postulate a dysontogenetic origin from rete blastema for them.

ADENOCARCINOMA ARISING IN A DIVERTICULUM OF THE FEMALE URETHRA

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AND
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THE LITERATURE of the past two decades reveals a steadily growing number of reported cases of primary carcinoma involving the female urethra. Walther,[1] in 1943, asserted that more than 275 cases were on record. Since that time, many more cases have been added to this list. As a result, cancer of the female urethra can no longer be considered rare, although it is still sufficiently uncommon to warrant comment. There are several excellent reviews dealing with the subject of cancer of the female urethra now available.[2]

The histological type of tumors found in the urethra is only casually referred to by a majority of authors, and there is little detailed information available. By far the commonest is epithelioma, either squamous or transitional cell varieties. Adenocarcinoma is seen much less frequently and has received scant attention. The only review found devoted entirely to this type of lesion is that published in 1947 by Walker and Huffman.[3] These authors, in a careful search of the literature, discovered but 27 authentic cases of adenocarcinoma of the female urethra, in addition to five other questionable cases. An incomplete survey of the most recent literature reveals two other unequivocal cases, reported by Seng and Siminovitch[2b] and Cuscaden,[4] appearing since the last case examined by Walker and Huffman,[3] bringing the total number of reported cases to 29, with five other questionable cases.

The case which we have observed is presented because the tumor arose in a diverticulum which was probably congenital in origin and because the histological characteristics of the tumor are unusual.

HISTORY OF CASE

Mrs. I. L. F., a woman aged 53 years, was first seen in February 1948, complaining that there had been irregular vaginal bleeding for about one year. Prior to this time her menses had always been regular, with an interval of 28 days and a duration of four to five days. Two weeks before admission a blood-stained vaginal discharge

From the Department of Pathology, Queen's University.

1. Walther, H. W. E.: J. Urol. **50**:380, 1943.

2. (*a*) Sparkes, T. P., and Parsons, W. H.: Urol. & Cutan. Rev. **41**:157, 1937. (*b*) Seng, M., and Siminovitch, M.: Canad. M. A. J. **58**:20, 1948. (*c*) Cosco, N. P.: M. Times, New York, **71**:122, 1943.

3. Walker, L. M., and Huffman, J. W.: Quart. Bull., Northwestern Univ. M. School **21**:115, 1947.

4. Cuscaden, W. G.: M. J. Australia **1**:487, 1944.

developed, which was continuous. Her past history appeared entirely irrelevant except for some constipation, stress incontinence and an appendectomy 25 years before. General physical examination at the time of first admission gave entirely negative results. Pelvic examination, however, revealed a cystic structure about 3 cm. in diameter located beneath the anterior vaginal wall. This proved to be a diverticulum, and a catheter could be passed easily into the urethra and then posteriorly through an opening into the diverticulum. This opening was approximately 2.5 cm. from the external meatus of the urethra. When the catheter was removed, considerable soft "brain-like" material adhered to the tip. Cystoscopic examination revealed the opening of the diverticulum easily, and roentgenographic visualization of the diverticulum filled with sodium iodide showed it to be about

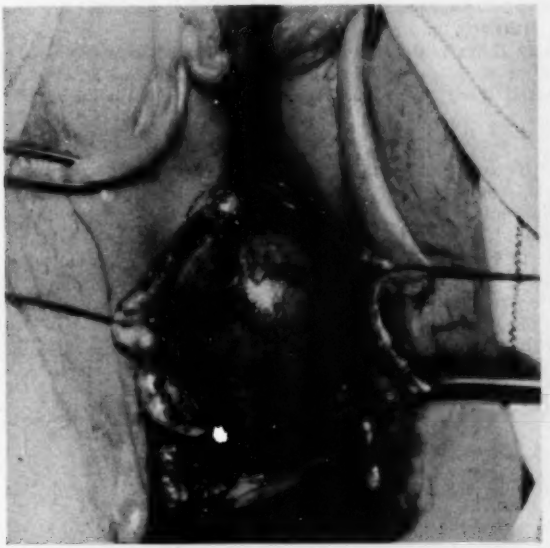

Fig. 1.—Appearance of the external genitalia during surgical removal of the diverticulum. The round mass in the center represents the diverticulum after incision of the overlying skin. Above can be seen a catheter in the urethra; below is the vaginal orifice; laterally are the labia minora and majora.

9 cm. in diameter. The soft tumor described was present in the diverticulum and appeared to be entirely confined to it.

Operative removal of the tumor was decided on. Prior to this procedure, roentgen radiation was applied to the area, with 1,000 r in divided doses applied to the center and directed toward each side. The right and left inguinal lymph nodes were removed for examination and showed no evidence of metastatic tumor. Surgical removal of the diverticulum and tumor was proceeded with (fig. 1), and after an uneventful postoperative recovery, the patient was discharged home in March 1948.

In June a follow-up examination showed the operative wound to be well healed, with no evidence clinically of recurrence of the tumor.

She was next seen in November, complaining of an occasional slight pinkish vaginal discharge. Examination now revealed a polypoid, gelatinous tumor 2 cm. in diameter, hanging from the anterior vaginal wall in the site of the operative scar and about 2.5 cm. from the external opening of the vagina. A catheter could be passed easily into the urethra. The growth was excised at its base and a portion sent to the laboratory for examination. No further treatment was undertaken at that time.

In March 1949 reexamination showed again that the tumor had recurred and, this time, presented as a large mass of soft tissue projecting into the vagina just inside the introitus and attached to the midportion of the urethra. The entire urethra was small and thickened, but there did not appear to be any ulcerative lesion of the mucosa. The tumor was removed by curetting, and specimens were taken from both the tumor and the urethra for biopsy; then 220 mg. of radium was applied to the area for a period of four hours.

In May 1949 a final follow-up examination showed some superficial ulceration on the right side of the urethra, but the thickening present earlier in the year had disappeared. There was little or no pain and no tenderness in the area.

GROSS EXAMINATION OF THE SPECIMEN

The specimen was that removed in February 1948. The main portion measured 3.5 by 3.0 by 1.9 cm. It consisted of a urethral diverticulum and adherent fibrofatty tissue. One surface was a rolling, grayish membrane, which was depressed in the central portion over an area of 2.0 cm., in the form of a crater, to a depth of 1.2 cm. Near one edge there were a number of rough, reddish tags. The other surface of the specimen was extremely irregular and rough, with many attached tags of fibrous tissue, adipose tissue and muscle.

Accompanying this specimen were fragments of tumor removed from the interior of the diverticulum when it was opened. They were irregular in shape and yellowish red in color and totaled 4.5 cm. in diameter. The consistency was very soft.

MICROSCOPIC EXAMINATION

All sections of the original tumor found within the cavity of the diverticulum, as well as those of the recurrent tumors in the vaginal wall, presented the same variable histological structure and arrangement. The following description applies equally to all sections studied.

The most striking feature of the tumor was the lacelike pattern, with spaces varying in size from small intracellular vacuoles to cysts as large as the low power field (fig. 2). The size of the spaces varied greatly from one area to another in the same section. The intracytoplasmic vacuoles varied from minute ones not causing any displacement of the nucleus to those large enough to occupy the whole cell and compress the nucleus into an elongated hyperchromatic crescent, such as one sees in a signet ring cell. In slightly larger spaces there was the suggestion that two or three such distended, vacuolated cells had fused to form a single cavity containing shreds of cytoplasm and lined by flattened endothelium-like cells. These spaces resembled minute cysts rather than acini. Still larger spaces had a circular form with a lining of flattened cells and resembled a lymphatic channel. The largest, cystlike spaces were irregular in contour and had a lining of cuboidal or low columnar cells. Between the cystlike spaces and channels there

were cords and sheets of cuboidal cells, many containing vacuoles of varying size, and separated by a mucoid stroma showing some lymphocytic infiltration. Many of the cavities of the spaces mentioned contained a clear-staining, lightly acidophilic material. In others the content was granular, sparse and acidophilic or appeared as fragmented strands attached to the cytoplasm of the lining cells. Occasionally there were one or more mononuclear cells within the space. These cells had round or oval, centrally placed nuclei, usually more compact and deeply staining than those of the lining cells, and fairly abundant, slightly granular, acidophilic cytoplasm. The lining of the cystlike spaces and cavities was variable. In many of the smaller ones there was a single layer of flattened, endothelium-like cells in which a crescentic and elongated, hyperchromatic nucleus with tapering ends had a thin strand of cyto-

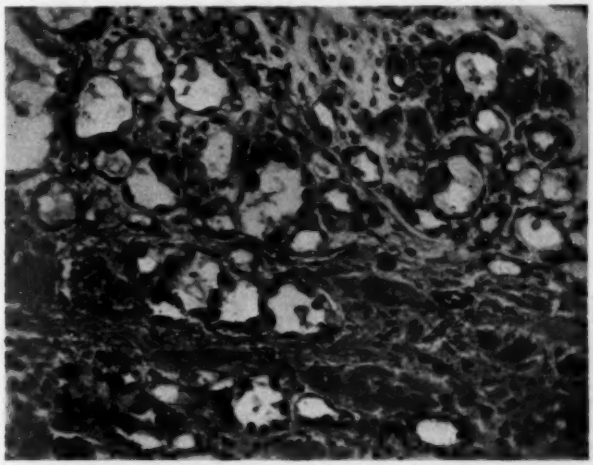

Fig. 2.—Primary tumor. Wall of diverticulum, showing cystlike spaces lined by flattened cells, endothelial in character, infiltrating muscle bundles.

plasm streaming out from each end to fuse with adjacent cells. At other times the nucleus was larger, less deeply staining, and oval, not spindle-shaped, and formed a bulge in the center of the cell. The larger cystlike spaces were often lined by cuboidal or low columnar cells in which there were no vacuoles and the oval vesicular nucleus was centrally placed. Many of the spaces had a lining which was several cell layers in thickness, the cells being cubical, low columnar or of pavement type, but this was difficult to determine because the superficial lining cells merged with sheets and cords of cells in which minute spaces, pseudoacini and vacuoles could be seen. The cytoplasm of the cells was variable, being for the most part acidophilic and slightly granular. In the more cellular, less vacuolated areas, it was faintly basophilic. In those cells lining spaces, no cilia could be seen, but strands and fragments of cytoplasm often appeared, protruding into the cavity and giving

the lining a ragged appearance. No basement membrane could be seen supporting lining cells or separating them from adjacent tumor cells or connective tissue stroma.

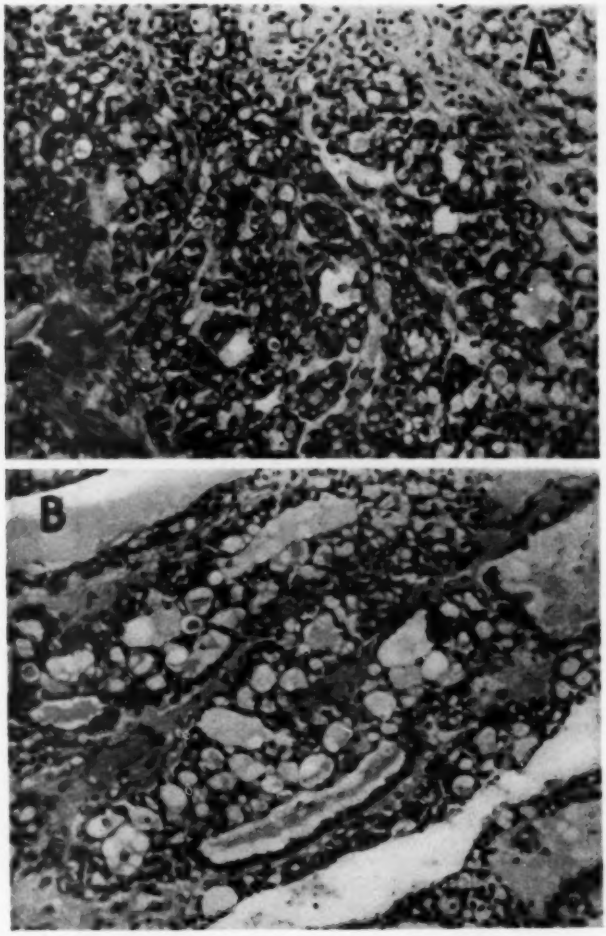

Fig. 3.—*A*, recurrent tumor showing irregular pseudoacinus and cyst formation. *B*, different area of same section as *A*.

The nuclei showed marked variation in size, shape and staining qualities. In those cells arranged in sheets and having no cytoplasmic vacuoles, they were oval or round, and vesicular, with a variable amount

of chromatin. In the less cellular areas the chromatin was denser and scattered throughout the nucleus, which was often hyperchromatic. In others, the chromatin was sparser, and nucleoli could be seen. Although the majority of cells contained only one large, deeply staining nucleolus, in a few cells as many as three were present. In the most highly cellular areas, many cells were seen with a very large nucleus containing only shreds and granules of chromatin at the periphery, with no nucleolus. The variation in size and shape of the nucleus was marked. Some elongated and hyperchromatic forms were seen, in cells which did not contain vacuoles and which did not line spaces. Mitotic figures were sparse in the original tumor and more frequent in the recurrences.

The stroma of the original tumor within the cavity of the diverticulum consisted of a fine collagenous fibrous tissue, very scant, containing

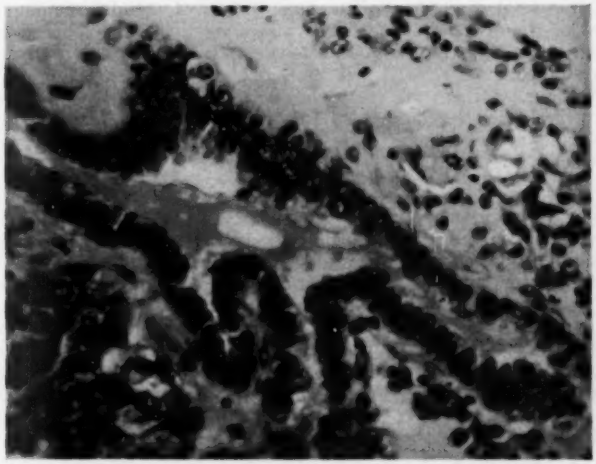

Fig. 4.—Recurrent tumor under high power magnification.

thin-walled blood channels. Between groups of cystlike spaces and sheets of tumor cells there was a very loose mucoid-appearing stroma, lightly infiltrated with lymphocytes. In the recurrent tumors (figs. 3 and 4) this same mucoid material was seen in some areas, but there was a more definite and denser fibrous tissue stroma containing blood vessels. The lymphocytic infiltration was still present.

Sections stained by the mucicarmine method revealed only scattered droplets staining a bright red. These were situated within some of the intracytoplasmic vacuoles as well as within some of the spaces, but on the whole the amount of mucin present was scant. The clear, faintly acidophilic material within the spaces stained pinkish brown for the most part. Stains for collagen did not reveal any collagen being formed by tumor cells. Reticulum stains revealed a very delicate network which surrounded groups of tumor cells, pseudoacini and cysts,

giving the tumor an alveolar appearance. No reticulum was seen between individual tumor cells.

Sections of the wall of the diverticulum revealed tumor cells of the same type as those described above, in that there were clusters of small spaces lined by flattened cells, situated in and just beneath the lining of the diverticulum and also deeper in the wall between the muscle bundles. The lining of the diverticulum consisted of the same sort of cells, often cuboidal or columnar in shape, at other times flattened and elongated, and two to three cell layers in thickness. At one point the elongated lining cells were many layers in thickness but had their long axis at right angles to the surface. They resembled fibroblasts in appearance and blended with the underlying fibrous connective tissue.

It must be noted that the wall of the diverticulum was composed of bundles of smooth muscle separated by interstitial connective tissue. The muscle bundles were large, formed a thick layer and appeared to run in several directions. The inner lining of the diverticulum consisted of tumor cells as described above, resting on a loose layer of fibrous connective tissue. No mucous glands were seen in several sections studied.

Sections of the wall of the urethra, from a specimen taken for biopsy in March 1949, revealed tumor invading the interstitial fibrous tissue and muscle bundles. The character of the tumor remained as described above.

COMMENT

The diverticulum in this case appeared to be of congenital origin in that it was large, with a thick muscular wall, not unlike that of the bladder, and the patient gave a long history of stress incontinence only, with no history of trauma or infection of the urinary tract. Considerable confusion and disagreement exist as to the origin of diverticula of the female urethra. In many cases, in which there was a history of childbirth and repeated urinary infection, they were thought to be acquired (Johnson,[5] Downer and Virgilio[6]). The only case in the literature which resembles the present one is that reported by McMahon,[7] who described a muscular wall in a large diverticulum similar to the one herein described.

The tumor found within the diverticulum resembled adenocarcinoma in most respects, in that there were spaces resembling acini and the cells were for the most part cuboidal in type. There was, however, a very striking tendency toward the formation of cystlike spaces of varying size, lined by flattened cells resembling endothelium. The production of mucus was scant. The latter features are not those usually found in adenocarcinoma. Histological descriptions of the 29 cases of adenocarcinoma of the female urethra referred to above are incomplete, but from the descriptions of several quoted by Walker and Hoffman,[3] they do not resemble the present case very closely, in that the tumors were clearly columnar cell adenocarcinoma.

It is our opinion that the tumor found in the diverticulum has many characteristics in common with those described by Masson, Riopelle

5. Johnson, C. M.: J. Urol. **39**:506, 1938.

6. Downer, I. G., and Virgilio, F. D.: J. Urol. **54**:53, 1945.

7. McMahon, S.: J. Urol. **55**:69, 1946.

and Simard [8] under the title of "Mésothéliome bénin de la sphère génitale," and by Golden and Ash [9] as "Adenomatoid Tumours of the Genital Tract." In both of the papers named, all the tumors described were considered as benign in character and were localized to the uterus and tubes or the spermatic cord and tunica vaginalis of the testicle. The histological structure of these benign tumors, however, showed the same canalicular and cystic arrangement, with sheets and cords of cells containing vacuoles of varying size. The lining cells were endothelial in character, with similar granular and acidophilic material and occasional mononuclear cells within the cavities of the spaces. The tendency toward formation of large cystic spaces with cuboidal and low columnar lining cells is also described. In the case herein described, the tumor was definitely malignant, and there were differences in cells and cellular arrangement in that no cilia were found and the cystlike spaces were often lined by several layers of cells, with a greater tendency toward the cuboidal and low columnar form. It is of course possible that such differences may be related to the cancerous character of the cells.

One can only speculate as to the most likely origin of the present tumor. It is possible that it arose from periurethral mucous glands. On the other hand, no mucous glands were found in the wall of the diverticulum, which, because of its thick muscular wall resembling bladder, is felt to be of congenital origin. Should the tumor be a cancerous variety of those described by Golden and Ash,[9] and Masson, Riopelle and Simard,[8] then its origin is even more debatable. Golden and Ash suggested that the tumors they described were epithelial in character and arose from misplaced nephrogenic tissue. In support of this, Kuhlenbeck [10] has recently shown that mesoderm derived from mesonephric duct may be present in the wall of the bladder and may give rise to adenoma or adenocarcinoma of the bladder wall. Masson, Riopelle and Simard, on the other hand, expressed the opinion that the tumors they described were of mesothelial origin, arising probably from misplaced peritoneal cell rests. Their evidence in support of this hypothesis is convincing.

Because the character of the cells is more definitely epithelial, with pseudoacinus and cyst formation and the production of mucus, albeit scant in amount, it is concluded that the tumor herein described is most probably adenocarcinoma, possibly arising from mucous glands.

SUMMARY

A case of a malignant tumor of a diverticulum of the female urethra is presented.

The diverticulum, because of its size, thick muscular wall and negative history, is considered to be of congenital origin.

The tumor, because of the predominantly epithelial character and arrangement of the cells, is probably adenocarcinoma.

Several possible origins for this tumor are discussed.

This case is published with the permission of Prof. E. M. Robertson, of the department of obstetrics and gynaecology of Queen's University.

8. Masson, P.; Riopelle, J. L., and Simard, L. C.: Rev. canad. de biol. **1**:720, 1942.

9. Golden, A., and Ash. J. E.: Am. J. Path. **21**:63, 1945.

10. Kuhlenbeck, H.: Personal communication to the authors.

General Reviews

TUMORS OF THE HEART

Review of the Subject and Report of One Hundred and Fifty Cases

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TUMORS of the heart are rarely diagnosed before autopsy, largely because there is little knowledge of their natural history. Surgical treatment of these neoplasms is virtually unheard of, and the present state of diagnosis is far behind the therapeutic possibilities. The commonest primary tumor has never been diagnosed ante mortem; most of the rare antemortem diagnoses have been those of metastatic growths. Several authors have wholeheartedly subscribed to the view that the diagnosis of cardiac tumors is either impossible or a matter of chance. Seen from the threshold of an era of ever bolder cardiac surgery, these tumors present a dismal diagnostic prospect. To aid in a better understanding of the problem, this paper presents a general discussion of tumors of the heart, together with a report of 146 secondary and four primary cardiac neoplasms.

The English literature has not contained a general review of cardiac tumors for 20 years, since Yater's [1] discussion of the subject in 1931. Numerous incomplete reviews have accompanied case reports since that time. Whorton [2] reviewed the sarcomas in 1949 and tabulated the cases reported to that year. The most comprehensive recent treatment of the subject is the exhaustive monograph in French by Mahaim,[3] of Lausanne, Switzerland. It is based on a considerable personal experience and gives a bibliography of 1,298 references. Aside from the obviously primitive state of the antemortem diagnosis of cardiac neoplasms, one finds few attempts at critical evaluation of the various tumors, and many of the controversial issues are dealt with now in the same fashion as they were in the early years of the present century. The examination of only one variety of cardiac tumor does not give the perspective required for a thorough understanding. In this belief that the particular must be considered in the light of the many, each type of tumor is reviewed at least briefly.

METASTATIC TUMORS

Metastatic tumors of the heart occur with approximately 20 to 40 times the frequency of primary growths. The interest inherent in these neoplasms is limited, but several considerations make their study imperative. They must be

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1. Yater, W. M.: Tumors of the Heart and Pericardium: Pathology, Symptomatology and Report of 9 Cases, Arch. Int. Med. **48**:627-666 (Oct.) 1931.

2. Whorton, C. M.: Primary Malignant Tumors of the Heart, Cancer **2**:245-260, 1949.

3. Mahaim, I.: Les tumeurs et les polypes du cœur: Etude anatomoclinique, Paris, Masson & Cie, 1945.

distinguished from primary tumors, they sometimes produce significant clinical findings, and they are of prognostic import.

Several reviews of the subject of metastatic heart tumors are available, most with clinical commentary.[4] The diagnosis has been made ante mortem in about 20 cases, usually on the basis of cardiac irregularities appearing in a patient with widespread tumor. One feels that thorough routine cardiac examinations of patients dying of cancer would yield evidence of metastasis to the heart oftener than the rarity of antemortem diagnoses indicates, although little would be gained thereby.

At present 4,375 autopsies on patients dying of cancers are recorded with the Harvard Cancer Commission. Of this number, 146 demonstrated metastases in the myocardium, an incidence of 3.4 per cent. Table 1 gives the distribution of these tumors as to general grouping and primary site. Other series of autopsies

TABLE 1.—*Relative Number of Cases of Tumors of the Heart, with Distribution According to Primary Site*

Total Cases 4,375		Total Cardiac Metastases 146
Carcinoma	102	
Sarcoma	26	
Cancerous melanoma	18	
Primary Sites		
Carcinoma		
Breast	23	
Lung	16	
Stomach	9	
Cervix uteri	7	
Kidney	7	
Tongue	6	
Rectum	4	
Penis	3	
Esophagus	3	
Ovary	3	
Testis, bladder, mouth, 2 each		
Vagina, liver (hepatoma, cholangiocarcinoma), prostate, thymus, lip, antrum, branchial cleft, pharynx, uterus, thyroid, sigmoid, scrotum, pancreas—1 each		
Sarcoma		
Lymphatic system	18	
Bone	2	
Penis, stomach, kidney, peripheral nerve, spleen, undetermined—1 each		
Melanoma		
Skin	12	
Eye	4	
Vulva	1	
Anus	1	

on patients with cancer of various types show both higher and lower incidence of cardiac involvement. Scott and Garvin[4b] found 101 cases in 1,082 autopsies. Burke's[5] series of 327 cases yielded 14 instances. Willis[6] records 20 instances in 323 autopsies. Pollia and Gogol[7] noted 29 secondary tumors in 1,450 autopsies. In Ritchie's[4d] 857 autopsies 16 cases were found. The totals of these various

4. (*a*) Lisa, J. R.; Hirschhorn, L., and Hart, C. A.: Tumors of the Heart: Report of 4 Cases and Review of Literature, Arch. Int. Med. **67**:91-113 (Jan.) 1941. (*b*) Scott, R. W., and Garvin, C. F.: Tumors of the Heart and Pericardium, Am. Heart J. **17**:431-436, 1939. (*c*) Siegel, M. L., and Young, A. M.: Electrocardiographic Findings in Tumors of the Heart with a Report of a Case, ibid. **8**:682-690, 1933. (*d*) Ritchie, G.: Metastatic Tumors of the Myocardium: A Review of 16 Cases, Am. J. Path. **17**:483-491, 1941. (*e*) Doan, J. C., and Pressman, R.: Antemortem Diagnosis of Tumors of the Heart, Am. J. M. Sc. **203**:520-524, 1942.

5. Burke, E. M.: Metastatic Tumors of the Heart, Am. J. Cancer **20**:33-47, 1934.

6. Willis, R. A.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, Ltd., 1933, pp. 259-268.

7. Pollia, J. A., and Gogol, L. J.: Some Notes on Malignancies of the Heart, Am. J. Cancer **27**:329-333, 1936.

series with my own show cardiac metastases occurring 326 times in 8,414 autopsies on patients with cancers, an incidence of 3.9 per cent.

The spectrum of primary sites for tumors metastasizing to the heart is wide, and cancers of all major organs have been reported as sources.[1] In our series cancers of the breast, lymphomas, cancerous melanomas and lung cancers lead the list. Among the single cases listed in table 1 are such unusual tumors as sarcoma of the penis, cholangiocarcinoma and sarcoma of the kidney. In only one instance was the cardiac metastasis the sole metastasis. In that instance the coronary arteries contained embolic tumor cells from a primary lung carcinoma.

In the heart metastases usually appear as discrete nodules, the morphologic aspect of which is similar to that of metastatic nodules elsewhere in the body. A great variety of gross appearances is seen, depending on the degree of involvement and the type of tumor. There are no outstanding features which permit one to identify the primary site from the appearance of the cardiac metastasis with the possible exception of a pigmented metastasis of cancerous melanoma. The nodules sometimes grow sufficiently large to encroach on the chambers, but this is rarely significant. Carcinomatous lymphangitis, usually from the breast or the lung, is striking but rare. Valvular implantation is the most unusual form of metastasis,

TABLE 2.—*Sites of Metastatic Tumors of the Heart in One Hundred Cases*

Both sides	38
Right side of heart	34
Left side of heart	14
Chiefly right side of heart	6
Septums	6
Apex	2

and the lesions sometimes resemble those of vegetative endocarditis. Involvement of the pericardium occurs together with that of the heart in a small percentage of the cases. Fibrinous pericarditis is often associated with tumor involvement of the epicardium. The microscopic appearance of the metastatic nodules in the heart does not differ from that of metastases in other organs.

In our series the right side of the heart was involved more frequently than the left, and when the cardiac metastases were widespread the right side of the heart was often the seat of greater involvement. Table 2 presents the distribution of these tumors in 100 cases in which the location of the metastases was described in detail. A predilection for the right side was also noted by Yater. Other observers have found the incidence equal, or involvement of the left side more frequent. Herbut and Maisel,[8] reporting 35 metastatic growths, found them equally distributed between the two sides. Scott and Garvin,[4b] in 101 cases of metastatic tumor, found left-sided involvement slightly more frequent. In Willis' 20 patients the distribution between the sides was equal. Involvement of the right side of the heart was sufficiently more frequent in the present group to invite explanation. Yater credited Windholz with first pointing out that Kretz's work finds application here. Kretz [9] injected fluid into the coronary arteries and

8. Herbut, P. A., and Maisel, A. L.: Secondary Tumors of the Heart, Arch. Path. **34**:358-364 (Aug.) 1942.

9. Kretz, J.: Über die Bedeutung der Venae minimae Thebesii für die Blutversorgung des Herzmuskels, Virchows Arch. f. Path. Anat. **266**:647-675, 1928.

found that roughly 75 per cent of the coronary arterial flow returned to the right chambers of the heart, passing through the thebesian veins and coronary veins. Embolic tumor cells may thus have more opportunity to lodge on the right than on the left. The relative avascularity of the cardiac valves is probably a major factor in the rarity of their involvement.

Cardiac metastasis occurs by three routes, embolic, lymphatic and direct invasion. The relative frequency of these types in the present series is in the order listed, even in the case of tumors of the lung and the breast. Several factors probably operate to keep the incidence of cardiac metastases low—strong kneading action, the metabolic peculiarities of striated muscle, rapid blood flow and restricted lymphatic connections. The blood flow[10] of the coronary system is among the highest in the body. The oxygen consumption per minute is very high (7.8 cc. per 100 Gm.), averaging over twice that of the brain (3.3 cc. per 100 Gm.). The lymphatics of the heart, divided into a superficial and a deep group, join and drain through two trunks into the tracheobronchial lymph nodes.[11] Metastasis via the lymphatic route is therefore against the direction of flow.

PRIMARY TUMORS

To the pathologist primary tumors of the heart are of much more interest than the secondary growths. The heart does not differ from any other mass of striated muscle and connective tissue in the variety of tumors it gives rise to; the gamut of benign and cancerous mesenchymal tumors is represented in the literature. Even teratoid tumors and so-called hamartomas have been reported, and a benign cyst with a calcified wall has been successfully removed surgically by Beck.[12] Although primary carcinoma has not been reported, there is reason to believe it may occur. The subject will be discussed here under six headings: myxoma, sarcoma, angioma, rhabdomyoma, fibroma and hamartoma, and miscellaneous tumors.

Myxoma.—This is the most frequent primary tumor of the heart and has excited the most controversy. It is a benign growth constituting nearly 50 per cent of the primary cardiac tumors. For many years the neoplastic nature of the tumor has been suspect, and it remains so to the present time. It is difficult to determine exactly when the controversy concerning the true nature of myxoma arose. Early reports based on gross appearance alone seem to have confused the issue.

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10. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, J. Clin. Investigation **27**:476-483, 1948. Bing, R. J.; Hammond, M. M.; Handselman, J. C.; Powers, S. R.; Spencer, F. C.; Eckenhoff, J. E.; Goodale, W. T.; Hafkenshiel, J. S., and Kety, S. S.: The Measurement of Coronary Blood Flow, Oxygen Consumption and Efficiency of the Left Ventricle in Man, Am. Heart J. **38**:1-24, 1949. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, Williams & Wilkins Company, 1943, pp. 250, 369 and 464.

11. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 24, Philadelphia, Lea & Febiger, 1942, pp. 359 and 721.

12. Beck, C. S.: An Intrapericardial Teratoma and a Tumor of the Heart: Both Removed Operatively, Ann. Surg. **116**:161-174, 1942.

At the time of Yater's review "about 75" myxomas had been reported, and he added two. Since his report an additional 49 cases [13] have been located in

13. (*a*) Chiari, H.: Myxom des rechten Vorhofs: Plötzlicher Tod durch Geschwülstembolie der Lungenschlagader, Centralbl. f. allg. Path. u. path. Anat. **52**:241-246, 1931. (*b*) Müller, W.: Über polypöse, bösartige, metastasierende Endokardgewächse und gewächsartige Thromben des linken Herzvorhofs (Case 2), Virchows Arch. f. path. Anat. **284**:105-119, 1932. (*c*) Bacaloglu, C.; Iliescu, C., and Raileanu, C.: Les thrombus myxoïdes du cœur, Presse méd. **41**:2074-2076, 1933. (*d*) Jaleski, T. C.: Myxoma of the Heart Valves, Am. J. Path. **10**:399-406, 1934. (*e*) Lymburner, R. M.: Tumours of the Heart: Histopathological and Clinical Study, Canad. M. A. J. **30**:368-373, 1934. (*f*) Jensen, C. R.: Fibromyxoma of the Left Auricle, Northwest Med. **33**:394-395, 1934. (*g*) Gorlitzer, V.: Myxom des Herzens mit multiplen Gehirnembolien, Centralbl. f. allg. Path. u. path. Anat. **61**:115-117, 1934. (*h*) Gilchrist, A. R., and Millar, W. G.: Paroxysmal Auricular Tachycardia Associated with a Primary Cardiac Tumor, Edinburgh M. J. **43**:243-258, 1936. (*i*) Bien, C. W., and Ch'in, K. Y.: Myxoma of Heart: Case Report and Review of Literature, Chinese M. J. (supp.) February 1936, pp. 64-72. (*j*) Fossel, M.: Beitrag zur Kenntnis der primären Herzgeschwülste, Frankfurt. Ztschr. f. Path. **49**:355-361, 1936. (*k*) Clerc, A.; Gauthier-Villars, P.; Delamare, J., and Roge: Un cas de tumeur myxoïde siégeant dans l'oreillette droite, Arch. d. mal. du cœur **30**:361-375, 1937. (*l*) Laubry, C.; Soulié, P., and Dugas, J.: Thrombose auriculaire gauche primitive à forme pseudo-tumorale, ibid. **30**:481-490, 1937. (*m*) Riopelle, J. L.: Sur un cas de myxome du cœur avec érythropoïèse locale (Considérations sur l'érythropoïèse et la mégacaryopïèse dans les thrombus), Ann. d'anat. path. **14**:725-751, 1937. (*n*) Bennett, D. W.; Konigsberg, J., and Dublin, W.: Primary Tumor of the Heart Producing an Unusual Cardiac Shadow in the Roentgenogram: Report of a Case, Am. Heart J. **16**:117-122, 1938. (*o*) Strouse, S.: Primary Benign Tumor of the Heart of 43 Years' Duration, Arch. Int. Med. **62**:401-412 (Sept.) 1938. (*p*) Kalbfleisch, H. H.: Weisse Hirnerweichung durch Gewebsembolus aus einem sogenannten Myxom des linken Herzvorhofes, Ztschr. f. Kreislaufforsch. **30**:625-632, 1938. (*q*) Fawcett, R. E. M., and Ward, E. M.: Cardiac Myxoma: A Clinical and Pathological Study, Brit. Heart J. **1**:249-260, 1939. (*r*) Dexter, R., and Work, J. L.: Myxoma of the Heart, Arch. Path. **32**:995-999 (Dec.) 1941. (*s*) Hoffman, M.: Cardiac Myxoma, Simulating Subacute Bacterial Endocarditis, Minnesota Med. **24**:585-586, 1941. (*t*) Salvador Junior, A.: Tumor mixóide da auricula esquerda, Folia anat. univ. conimb. (art. 4) **16**:1-14, 1941. (*u*) Behr, E.; Van der Reis, M., and Meyler, L.: Myxoma cordis, Nederl. tijdschr. v. geneesk. **85**:3453-3460, 1941. (*v*) Kirsten, L.: Myxoma endocardii, unter dem Bilde einer Endocarditis lenta verlaufend, Acta med. Scandinav. **109**:77-80, 1941. (*w*) Ringertz, N.: Über sogenannte Endokardmyxome, Acta path. et microbiol. Scandinav. **19**:262-299, 1942 (same case as *v*, with pathology discussion). (*x*) Orr, J. W.: Endothelioma (Pseudomyxoma) of the Heart, J. Path. & Bact. **54**:125-128, 1942. (*y*) Hamilton-Paterson, J. L., and Castleden, L. I. M.: Intracardiac Tumors, Brit. Heart J. **4**:103-114, 1942. (*z*) Mahaim, I.: Myxome microscopique de la cloison chez fillette de 3 mois, bloc auriculo-ventriculaire 3:1, Helvet. med. acta **10**:129, 1943. (*a'*) Thompson, R. B.: A Case of Myxoma of the Left Auricle, Brit. Heart J. **6**:23-26, 1944. (*b'*) Burnett, W., and Davidson, J. I.: A Case of Myxoma of the Heart, ibid. **7**:180-182, 1945. (*c'*) Field, M. H.; Donovan, M. A., and Simon, H.: Primary Tumor of the Left Auricle Simulating Mitral Stenosis, Am. Heart J. **30**:230-245, 1945. (*d'*) Straus, R., and Merliss, R.: Primary Tumor of the Heart, Arch. Path. **39**:74-78 (Feb.) 1945. (*e'*) Brown, W. O.: Myxoma of Heart, Am. Heart J. **31**:373-375, 1946. (*f'*) Anderson, W. A. D., and Dmytryk, E. T.: Primary Tumor of the Heart Containing Epithelium-like Elements, Am. J. Path. **22**:337-349, 1946. (*g'*) Young, R. D., and Hunter, W. C.: Primary Myxoma of the Left Ventricle with Embolic Occlusion of Abdominal Aorta and Renal Arteries, Arch. Path. **43**:86-91 (Jan.) 1947. (*h'*) Thys, H.; Beccol-Livensac, J., and Monie, J.: Polype auriculaire silencieux (thrombo-myxome), Arch. d. mal. du cœur **40**:147-152, 1947. (*i'*) Pariscenti, P.: Fibroangioelastoma dell'atrio sinistro, abstracted, Rev. di pat. e clin. **3**:1-13, 1948. (*j'*) Brewin, T. B.: Four Cases of Polypoid Tumor (Myxoma) Within the Left Auricle of the Heart, Guy's Hosp. Rep. **97**:64-74, 1948. (*k'*) Weinstein, M. S., and Arata, J. E.: Mitral Stenosis and Insufficiency Produced by Cardiac "Myxoma," Am. Heart J. **38**:781-787,

the available literature, and two are added here. Sixteen articles were not available for review. The total of reported cases is therefore approximately 125. A recent article gives the total as near 200.[13j'] In the cases reviewed the age range was from 3 months to 68 years, with the majority between 30 and 60 years. The sex distribution was equal.

Clinically the myxomas have often been associated with signs of mitral stenosis. A history of frequent fainting spells may be obtained. Occasionally, suggestive changes in symptoms have been noted with variations in the patient's posture. Relentless cardiac failure occurring in young persons without any of the usual etiological factors has been a common history. The lack of response to digitalis is considered important by Yater and others. Emboli from the tumors have been found in the brain,[14] the lungs,[13a] the aorta,[13g'] the renal arteries [13g'] and the extremities,[13k'] with corresponding symptoms and signs. Sudden death has been reported due to pulmonary embolism from a myxoma of the right auricle.[13a] One patient presented paroxysmal auricular tachycardia.[13h] Two have had signs of subacute bacterial endocarditis—peripheral embolic manifestations, low grade fever and changing heart murmurs; both had sterile blood cultures.[15] One of these patients was the only one who had a definite history of rheumatic fever.[13v] One patient had signs of heart disease for 43 years, all presumably on the basis of myxoma.[13o] The clinical features of the tumor are discussed in several papers.[16] No myxoma has been diagnosed during the life of the patient.

Myxomas are found almost exclusively in the atriums; roughly 75 per cent occur in the left atrium. Their localization is even more specific in that almost all of them attach to, or overlie, the fossa ovalis or its rim. In the last 49 cases one tumor arose on a valve, and one in the left ventricle. Most of the tumors have nearly filled the atrium and have produced some degree of dependent obstruction of the mitral or the tricuspid valve. One was microscopic in size, and a few have exceeded 10.0 cm. in maximum dimension. The tumors have been entirely intracavitary except in one instance.[13z] They are usually polypoid (80 per cent), are frequently pedunculated and are externally smooth or gently lobular, often with polypoid projections. Occasionally they are villous. Their consistency varies with their collagen content and has been variously described as gelatinous, soft, rubbery, firm or resilient. They are white, yellow-white, yellow or light brown and frequently display areas of hemorrhage. Thrombi sometimes overlie the surface of the tumor. The external surface may be indented when the growth has prolapsed through a valve orifice. The heart weight is usually normal or slightly increased, although several tumor-bearing hearts have weighed between 700 and 800 Gm.

Microscopically, the average tumor is described as poorly cellular, covered by unbroken endocardium and composed of loose tissue of varying vascularity. Giant and multinucleate cells are scattered throughout, but mitoses are not seen. Stellate

1949. (*l'*) Macoun, S. J. R.: Cardiac Myxoma, Thorax **4**:39-43, 1949. (*m'*) Allison, D. R., and Susman, W.: Myxoma of the Heart, Lancet **2**:11-12, 1949. (*n'*) Von Reis, G.: Clinical Aspects of Endocardial Myxoma Situated in Left Atrium, Acta med. Scandinav. **133**:214-219, 1949. (*o'*) Coulter, W. W., Jr.: Myxoma of the Heart (Left Auricle), Arch. Path. **49**:612-617 (May) 1950.

14. Gorlitzer.[13g] Kalbfleisch.[13p] Brown.[13e']

15. Hoffman.[13s] Kirsten.[13v]

16. Yater.[1] Gilchrist and Millar.[13h] Fawcett and Ward.[13q] Hamilton-Paterson and Castleden.[13y] Von Reis.[13n']

cells occur sporadically. The blood vessels are of capillary size for the most part, and their lining cells are plump and often multilayered. Larger vessels with thick walls are frequent and occasionally are thrombosed. Hemorrhages involving the stroma are common, and hemosiderin is found in varying amounts, both free and in macrophages. Lymphocytes and plasmacytes are almost always present, with occasional focal collections. Mucin stains are often positive in all or part of the matrix. Cysts lined by epithelium have been found. Bone and marrow are described in the tumors. Collagen deposition is variable. Stains for elastic tissue frequently reveal large numbers of those fibers focally or throughout the tumor. The medial elastic fiber network of the endocardium is intact where it has been described.

The appearances described above explain the various diagnostic terms which have been applied to these tumors: myxoma, myxofibroma, elastomyxoma, fibroangiomyxoma, hemangioelastomyxoma and fibroelastomyxoma.

No evidence has been presented indicating that a significant number of these tumor-bearing hearts have been injured by a recognized disease process other than the primary one. One patient had a history of rheumatic fever [13v] but no pathological evidence of that disease. Another patient, aged 46 years,[13y] was said to have had "cardiac trouble" since an attack of "flu" at age of 15, but was later accepted for military service. The case of Dexter and Work [13r] presented equivocal findings of endocardial damage which those authors felt were clearcut evidence of extinct rheumatic fever. These are described thus:

> . . . There were slight shortening and marginal thickening of both mitral leaflets, and the chordae tendineae attached to them were mildly thickened, shortened and occasionally fused. The aortic leaflets were slightly thickened at the base of their attachment and showed slight firm fibrous submarginal adhesions in the commissures.

The patient was a 53 year old woman with no history of rheumatic fever. It is difficult to accept this slight evidence as unequivocal indication of rheumatic fever. No report mentions more established stigmas of acute or remote rheumatic fever, such as Aschoff bodies, vascularization of valves, marked valvular endocarditis and thickening of chordae tendineae, or pericardial adhesions and thickening.

Maun [17] reported a "polypoid thrombus of the left auricle" which has many characteristics which would justify including it in the myxoma group of tumors. The heart of his patient showed coronary sclerosis and myocardial fibrosis as well as a left auricular mass. Large blood vessels entered the tumor from deep within the endocardium. The thick walls of these vessels were interpreted by Maun as evidence of "disuse atrophy." He concluded that the appearance of these blood vessels, together with signs of damage to the auricular endocardium, indicated a non-neoplastic origin of the tumor. It seems reasonable that a tumor might regress and show thickening of its nutrient vessels, and it is unusual for a plexus of thick-walled blood vessels to form in the endocardium underlying a thrombus.

With the above characteristics in mind, the arguments relating to the true nature of these tumors may be examined. Thorel [18] stated that patients with myxomas were all suffering from circulatory deficiency with thrombosis in other parts of the body; that the histologic descriptions given by most authors allow the diagnosis of organized thrombi; that there was no cogent reason to diagnose a neoplasm. His last article appeared in 1915, and his premises are not tenable on the basis of material

17. Maun, M. E.: Polypoid Thrombus of the Left Auricle, Am. Heart J. **26**:549-554, 1943.

18. Thorel, C.: Geschwülste des Herzens, Ergebn. d. allg. Path. u. path. Anat. **17** (pt. 2):667-687, 1915.

reported since that time. It is interesting to note that he had not seen any of these tumors himself but based his conclusions solely on what he had found in the literature. Husten,[19] in 1922, described a tumor in the right atrium with its base between the inferior vena cava and the wall of the atrium. It consisted of several hematomas in all stages of organization, was not homogeneous and presented the character of granulation tissue of partly fresh and partly older nature. He then reviewed 71 cases which he found in the literature and concluded that almost every tumor takes its origin in a thrombus, although in a few instances a neoplasm could not be ruled out. It should be noted that his description of his tumor is not that of myxoma as generally presented. Others have mentioned that imbibition of plasma by a thrombus and metaplasia of its stroma explain why these growths differ in appearance from the usual thrombus. Ringertz [12w] commented on the fact that portions of the tumors are similar to the growth of fibroblasts in a tissue culture.

The impression that myxomas are really thrombi therefore seems to have arisen in several ways: first, by failure to establish any criteria for myxoma or to distinguish between a myxoma and an obvious polypoid thrombus; second, by the presence in many myxomas of plump fibroblasts, hemosiderin and large numbers of capillaries; last, by the rarity of the tumors, and the consequent inability of any single observer to amass a large experience with them. The second point deserves explanation. Myxoma is a soft tumor subjected to considerable mechanical stress; hemorrhages and hemosiderin deposition may be expected to occur from capillaries in such a structure.

Against these arguments are many sound reasons for considering the myxomas true neoplasms. Ribbert [20] pointed out many of these, and others have added to his list. Most of the tumors are much larger than thrombi and are far less cellular. They do not retract in the fashion of thrombi elsewhere. They occur for the most part in hearts free of other disease. There is usually no evidence of damage to account for thrombosis. Almost all the myxomas are found in the atriums, especially the left, while thrombi occur with approximately equal frequency in the atriums and the ventricles. Most atrial thrombi are in the auricular appendage, and myxomas are not found in that location. There are no convincing intermediate stages between a frank thrombus and a myxoma, even in the pedunculated and ball valve thrombi found in the atriums. There is no evidence of stratification in myxomas, although almost all thrombi show it. Authors on each side of the argument have discussed the origin of the mucin that is seen in these tumors. The group favoring a thrombotic origin say mucin occurs in thrombi, and those favoring neoplasm say it occurs only in neoplasm. As Yater has observed, too much stress has already been laid on this point. The presence of mucin with the usual stains indicates a particular type of mesenchymal tissue, whose frequent presence in the tumors is generally admitted. It is not specific for either thrombi or myxomas.

Ribbert, who strongly championed the neoplastic nature of myxoma, felt that the tumors arose from remnants of the myxoid tissue which composes the embryonic endocardium. In his experience the frequent persistence of such tissue about the fossa ovalis furnished an explanation for the peculiar localization of these tumors.

19. Husten, K.: Über Tumoren und Pseudotumoren des Endokards, Beitr. z. path. Anat. u. z. allg. Path. **71**:132-169, 1922.

20. Ribbert, H.: Die Endokardtumoren, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1924-1939, vol. 2, pp. 276-282 and 288-289.

Impressed by this definite predilection for the rim of the foramen, I undertook examination of this region in an unselected series of hearts. Fifty-five interatrial septums were obtained from the routine postmortem examinations of this department. Three to six sections were taken from each specimen to include the rim of the fossa ovalis in various planes. The sections were stained with hematoxylin and eosin and with periodic acid–Schiff's reagent. Myxoid tissue as such was not found. The subendocardial tissue of this region was often thicker and denser than that in other portions of the heart and possessed the same metachromatic properties. Even without special attention, it is apparent that there is more connective tissue within the heart in the interatrial septum than in any other part of the organ (fig. 1 *A*). More of this is in the flat (left) portion of the foramen than in the indented (right) side. In a few cases small irregular areas of loose fibrillar connective tissue were present between the flaps of the foramen. In four cases the endocardium showed minute areas in which there were lacunas of capillary size lined by plump endothelial cells (figs. 1 *B* and 2). Three of these structures were intracavitary, and one was subendothelial. Although their significance is doubtful, they were the only unusual finding which might conceivably be linked with the myxomas. These small endocardial malformations have not been noted elsewhere in the heart. Warren [21] suggested that they resemble an organizing pericardial exudate. There is an obvious resemblance between these structures and the capillaries of a myxoma. It will be recalled that the myxomas are almost always entirely intracavitary, with underlying intact medial elastic fiber network. Orr [13x] has suggested that the neoplastic part of a myxoma is the endothelial element and that the myxoid stroma is a degenerative phenomenon.

The mechanical stresses to which a soft tumor in a cardiac chamber is subjected are probably responsible for the tendency of these tumors to be myxoid. The effects of constant motion on proliferating connective tissue are well seen in human bone fractures, where cartilage forms in much larger amounts in poorly immobilized fractures than it does in well fixed fractures. In the two cases reported here the myxoid areas were most prominent at the base and edges of the tumor, where motion is greatest. Although these tumors have been named because of this myxoid tendency, the evidence indicates that it is of minor significance.

The myxomas are thus seen to form a uniform group of tumors occurring in a definite location in the heart and having a characteristic gross and microscopic appearance. Aside from bearing superficial similarities to some thrombi there is little to indicate that they are thrombi, or arise from them, and the bulk of evidence indicates that they are true neoplasms. My own study of 55 foramens did not reveal the myxoid rests said to occur in that area by Ribbert, but the region contains most of the connective tissue in the heart and might be expected to be the site of most connective tissue tumors. Mechanical factors are probably responsible for the frequent myxoid character of these connective tissue tumors. An endocardial deformity found in four of 55 foramens resembles the endothelial elements of the myxomas reported here.

Sarcoma.—Cardiac sarcomas closely follow the myxomas in numbers reported. An excellent review of the subject has recently been presented by Whorton,[2] and the

21 Warren, S.: Personal communication to the author.

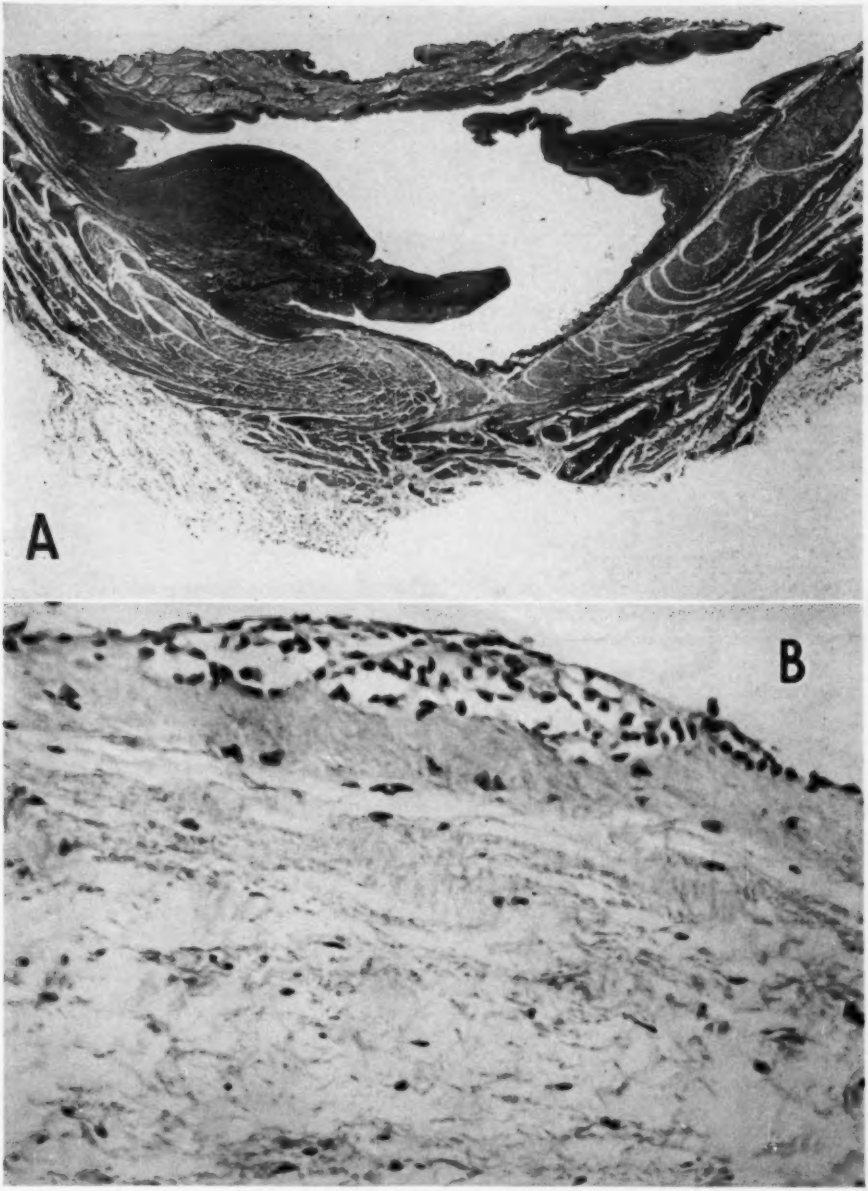

Fig. 1 (foramen ovale).—*A*, random section through folds of fossa ovalis, illustrating the relatively large amounts of connective tissue present in this area. Periodic acid–Schiff's reagent stain; × 11.85.

B, random section through a grossly normal foramen ovale showing a minute endocardial deformity. This consists of spaces lined by flattened cells, which project into the atrial cavity. Hematoxylin and eosin stain; × 338.5.

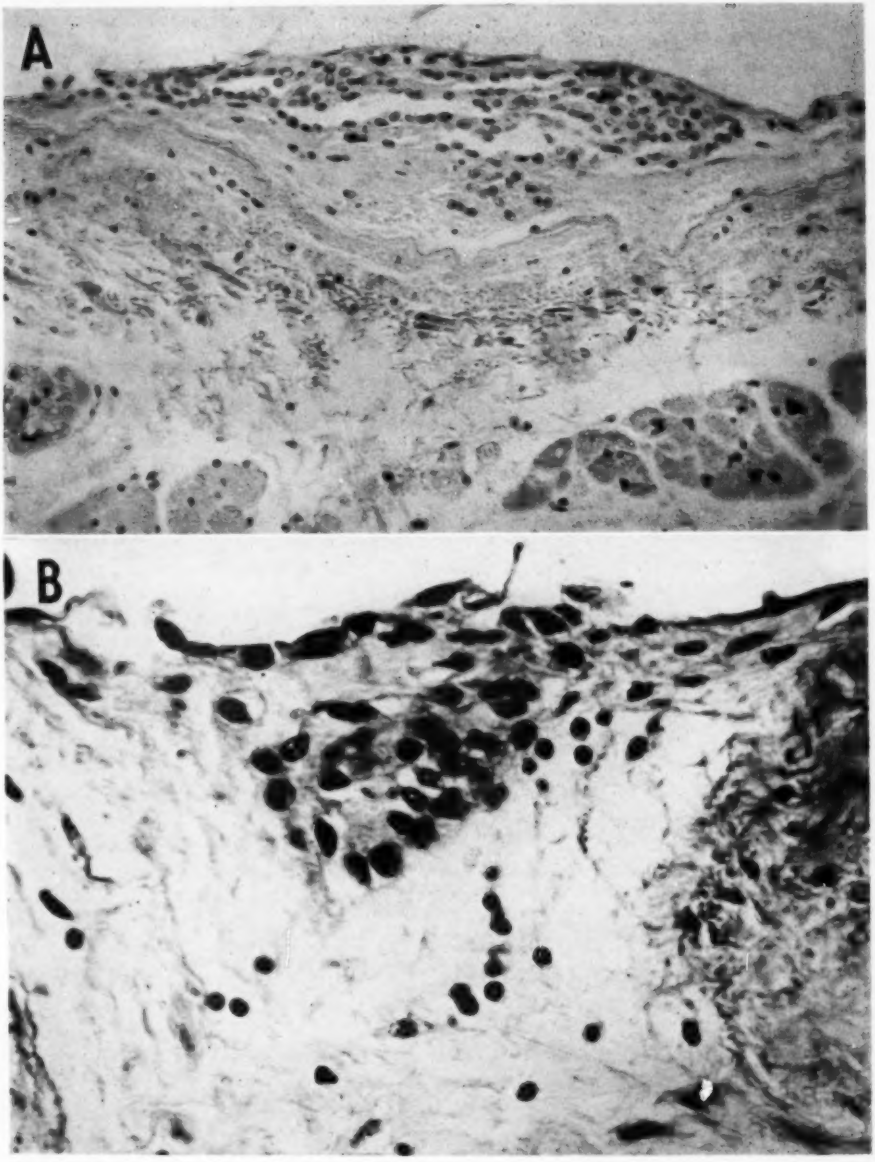

Fig. 2.—*A*, random section through a grossly normal foramen ovale showing a minute endocardial deformity. This consists of spaces lined by flattened cells, which project into the atrial cavity. Hematoxylin and eosin stain; × 254.

B, random section through a grossly normal foramen ovale showing a minute endocardial deformity. The spaces are in the subendothelial connective tissue. Hematoxylin and eosin stain; × 634.5.

discussion here will be brief. Whorton was able to collect 99 cases from the literature, to which he added one of his own. Thirteen cases may be added to his list from the literature,[22] and one [23] which he included may be considered benign. One case is presented here, bringing the present reported total to 113.

The age distribution of sarcomas of the heart is the same as that of sarcomas in general, and ranges from 3 days to 79 years. The sex distribution is approximately equal. The symptom complex is chiefly founded on the frequent location of the tumor in the right atrium.[3] In this position it may give rise to signs of obstruction of the superior vena cava. Hemopericardium is not infrequent and should arouse suspicion of cardiac cancer.[24] Bizarre disturbances in rhythm and rapid changes in the heart shadow on roentgenograms may be observed.

Five primary sarcomas of the heart have been diagnosed during the life of the patients. Popp [25] made the first correct diagnosis of a sarcoma of the right atrium. Barnes, Beaver and Snell [26] were the first to make such a diagnosis in this country. The cardiac manifestations in their patient were thought to be due to tumor after biopsy of a nodule in the deltoid muscle showed a sarcoma. Shelburne [24] relied on clinical findings for his correct diagnosis. The patient of Ravid and Sachs [27] had multiple mesenchymal tumors, a carcinoid of the rectum and three cardiac tumors. Lübschitz, Lundsteen and Forchhammer [22m] used artificial pneumopericardium to outline their patient's heart on roentgen examination and were aided in their diagnosis by the tumor cells which were present in the pericardial effusion.

The heart weight is generally higher in cases of sarcoma than in cases of myxoma. A maximum of 2,700 Gm. is recorded,[22a] which is three times the maximum weight

22. (*a*) Newman, R.: An Unusual Tumor of the Heart, Memphis M. J. **22**:96-97, 1947. (*b*) Wells, A. H.; Rowe, O. W., and Joffe, H. H.: Diagnostic Case Study, Minnesota Med. **30**: 282-284, 1947. (*c*) Lange, H. F., and Christiansen, T.: Hemopericardium—Angiosarcoma Cordis; Case of Primary Heart Tumour, Diagnosed Intra Vitam, Acta med. Scandinav. **127**:107-115, 1947. (*d*) Amsterdam, H. J.; Grayzel, D. M., and Louria, A. L.: Hemangio-Endothelioblastoma of the Heart, Am. Heart J. **37**:291-300, 1949. (*e*) Adamson, W. W.: A Case of Primary Sarcoma of the Heart, J. Path. & Bact. **60**:344-346, 1948. (*f*) Halhuber, M. J., and Kapferer, J. M.: Über ein Endothelsarkom im Vorhof des linken Herzens, Cardiologia **13**:305-324, 1948. (*g*) Nunes-Petisca, J. L.: À propos d'un cas de sarcome du cœur chez un brebis, abstracted, Arq. de Pat. **20**:70-83, 1948. (*h*) Shelburne, P. A.: Primary Sarcoma of the Heart, with Report of a Case, Ann. Int. Med. **29**:1139-1148, 1948. (*i*) Cohen, H.: Primary Fibrosarcoma of the Heart with Metastases, New York State J. Med. **49**:1448-1449, 1949. (*j*) Walker, R. H.: Primary Sarcoma of the Heart, U. S. Nav. M. Bull. **49**:878-883, 1949. (*k*) Vanecek, E.: Primary Round Cell Sarcoma of the Heart, abstracted, Časop. lék. česk. **88**:389-391, 1949. (*l*) Fretheim, B.: Leiomyosarkomer i ventrikkel og tarm, abstracted, Nord. med. **41**:69-71, 1949. (*m*) Lübschitz, K.; Lundsteen, E., and Forchhammer, E.: Primary Malignant Heart Tumor Diagnosed in Vivo with the Aid of Artificial Pneumopericardium, Radiology **52**:79-87, 1949.

23. Fidler, R. S.; Kissane, R. W., and Koons, R. A.: Primary Fibrosarcoma of Heart, Am. Heart J. **13**:736-740, 1937.

24. Shelburne, S. A.: Primary Tumors of the Heart, with Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis Before Death, Ann. Int. Med. **9**:340-349, 1935.

25. Popp, L.; Über die Herzgeschwülste in Verbindung mit einem Falle von Sarkom des rechten Vorhofohres, Fortschr. a. d. Geb. d. Röntgenstrahlen **46**:23-28, 1932.

26. Barnes, A. R.; Beaver, D. C., and Snell, A. M.: Primary Sarcoma of the Heart: Report of a Case with Electrocardiographic and Pathological Studies, Am. Heart J. **9**:480-491, 1934.

27. Ravid, J. M., and Sachs, J.: Tumors of the Heart, with a Report of a Primary Fibromyxosarcoma of the Left Auricle and the Pulmonary Vein, Associated with Multiple Tumors of the Mesentery and Alimentary Tract, Am. Heart J. **26**:385-397, 1943.

of the benign group. The external appearance of the heart is frequently altered, and the pericardium is involved either directly or by adhesions in a large percentage. Over half of the tumors arise in the right side of the heart (62 cases), and they are equally distributed between the right atrium and the right ventricle. The tumors are usually infiltrative or sessile, but roughly 20 per cent [3] have polypoid structures projecting into the chambers. Distant metastases occur in over 30 per cent of the cases. Whorton gives the frequency of metastatic involvement of organs as in the order named: lungs, thoracic lymph nodes, liver, kidneys, pericardium, adrenals and pancreas.

Histologically, most of the tumors have been "spindle cell" sarcomas of some sort, including fibrosarcoma, fibromyxosarcoma, myxosarcoma and leiomyosarcoma. Next in frequency are the "round cell" neoplasms, designated either by that term or as lymphosarcoma, reticulum cell sarcoma or stem cell lymphoma. Rhabdomyosarcoma and varieties of angiosarcoma have been diagnosed many times. Choisser and Ramsey [28] described two cases as instances of Kaposi's disease primary in the heart and claimed that eight other reported cases fall into this group. Their distinction does not seem clear. It is difficult to subclassify these tumors because of the great variety of diagnostic terms and criteria used by the various authors. There also would seem to be little gained by doing so, since no clearcut subgroups have appeared on other than a histological basis. It is apparent that the gamut of mesenchymal cancers has been described.

The rarity of cancer of the heart is satisfactorily explained by consideration of the relative size of the organ and its normal structure. The heart constitutes from 0.4 to 0.5 per cent of the body weight, while the skeletal muscles form 40 per cent of the total.[12] Tumors of these organs might be expected to occur in numbers bearing the same relation as their weight. It is well known that there is little, if any, mitotic activity in heart muscle and that injuries result in degenerative, rather than regenerative, phenomena. The amount of connective tissue is small, but it probably shows more divisional activity than the muscle. There is no satisfactory explanation for the preponderance of cancer of the right side of the heart, but the number of cases is small and the differences are not overwhelming; so the distinction may be more apparent than real.

Angioma.—The number of benign angiomas reported as occurring in the heart is small, and only 12 appear in the literature under that name. The cancers that supposedly are of vascular origin have been included with sarcomas in general. A complicating element is present in the German literature of 30 years ago, where several authors refer to one group of these tumors as "varices of the heart," a matter which is discussed below.

The 12 reported angiomas [29] consist of five hemangiomas and seven lymphangiomas. Four of these tumors have produced complete heart block, and five have

28. Choisser, R. M., and Ramsey, E. M.: Angioreticuloendothelioma (Kaposi's Disease) of the Heart, Am. J. Path. **15**:155-178, 1939.

29. (*a*) Armstrong, H., and Mönckeberg, J. G.: Herzblock, bedingt durch primären Herztumor bei einem 5 jährigen Kinde, Deutsches Arch. f. klin. Med. **102**:144-166, 1911. (*b*) Lloyd, P. C.: Heart Block Due to Primary Lymphangioendothelioma of Atrioventricular Node, Bull.

proved fatal. Armstrong and Mönckeberg [29a] observed a 5½ year old boy with a lymphangioma near the origin of the bundle of His. Lloyd's [29b] patient, a 39 year old woman, had a lymphangioma involving the atrioventricular node. Grant and Camp [29c] found a hemangioma at the base of a tricuspid valve leaflet, between it and the orifice of the coronary sinus. Their patient was a 39 year old man. In the case of Perry and Rogers,[29d] which concerned a 24 year old woman who had had fainting attacks all her life, a lymphangioma was found on microscopic examination of the interatrial septum. Uehlinger's [29e] patient, a "nervous" 14 year old girl, had a regular pulse on one examination before she was found dead in bed. She had an extensive lymphangioma involving the interventricular septum and encroaching on the left anterior descending coronary artery.

The other angiomas were incidental findings. Escher's [29f] was a small (0.8 cm.) lymphangioma on the posterior cusp of the aortic valve. Forel [29g] found a pedunculated lymphangioma on the posterior leaflet of the mitral valve. Lymburner's [13e] patient was a 10 month old boy with a cystic hygroma of the neck and mediastinum; a separate lymphangioma was present on the surface of the right auricle. Rau [29h] described a cherry-sized cavernoma in the subendocardium of the right auricle, similar to Penneman's [29i] hemangioendothelioma of the anterior wall of the left atrium and Schuster's [29j] hemangioma on a papillary muscle of the right ventricle. Train [29k] found a similar tumor the size of a hazelnut in the interventricular septum.

Mönckeberg [30] expressed the opinion that the tumors cited in the last paragraph were not really "blastomas" but probably varices. He did not mention Escher's case, and Lymburner's was reported later. Several other authors have also held that such tumors are varices, not neoplasms. In 1922 Husten [19] collected 31 cases of varices from the literature, and three cases have been reported since that time.[31] The case reported here falls into this group.

The tumors described as varices are remarkably similar. They consist of multiple, or occasionally single, clustered, pink to red subendocardial nodules. Almost all of them are in the right atrium, on the posterior and inferior rim of the foramen ovale, and they are sessile or polypoid. Of the 35 reported, 26 were in the right atrium, 3 in the left atrium, 3 on the valves (2 tricuspid, 1 pulmonary), 2 on the anterior papillary muscle of the right ventricle, and 1 multiple in both ventricles.

Microscopically, they are composed of thin-walled blood vessels, where they have been examined. Often they contain a clot, or an organized thrombus, in one

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Johns Hopkins Hosp. **44**:149-154, 1929. (*c*) Grant, R. T., and Camp, P. D.: A Case of Complete Heart Block Due to an Arterial Angioma, Heart **16**:137-143, 1932. (*d*) Perry, C. B., and Rogers, H.: Lymphangio-Endothelioma of Heart Causing Complete Heart Block, J. Path. & Bact. **39**:281-284, 1934. (*e*) Uehlinger, E.: Die Lymphgefässgeschwülste des Herzens, Beitr. z. path. Anat. u. z. allg. Path. **78**:434-440, 1927. (*f*) Escher: Zur Kenntnis der primären Geschwülste des Herzens, Inaug. Dissert. Munich, 1909; cited by Uehlinger.[29e] (*g*) Forel, F. C.: Two Cases of Primary Neoplasm of the Cardiac Valves, Internat. Clin. **4**:147-158, 1919. (*h*) Rau, F.: Cavernöses Angiom im rechten Herz-Vorhof, Virchows Arch. f. path. Anat. **153**:22-29, 1898. Penneman, G.: Note sur un cas d'haemangio-endothéliome du cœur, Ann. Soc. de méd. de Gand **88**:57-66; 1908; cited by Yater.[1] (*j*) Schuster, H.: Haemangioma Cavernosum im Herzen eines Neugeborenen, Virchows Arch. f. path. Anat. **215**:335-339, 1914. (*k*) Train, cited by Mönckeberg.[30] Lymburner.[13e]

30. Mönckeberg, J. G., Erkrankungen des Myokards und des spezifischen Muskelsystems, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1924-1939, vol. 2, pp. 482-502.

31. Elaut, L.: Au sujet des varices du cœur, Rev. belge sc. méd. **4**:149-152, 1932.

or more lumens. The majority of them have been found in patients over 50 (perhaps because that is the age period when most patients come to autopsy).

Those using the term "varices" have felt that these vascular tumors represent dilated thebesian veins, which, they assert, open chiefly into the right side of the heart in the region where the tumors are commonest. Hypoplasia of a subendocardial vein and congenital narrowing of the orifices of thebesian veins have been suggested as etiological factors.

In the 55 foramen ovales examined during the preparation of this paper, subendocardial vessels were rarely seen. Only twice were vessels present which reached the size of a large capillary. The appellation "varices" does not seem too appropriate as used in connection with these tumors. It implies dilatation of vascular channels, which are not always to be found where the tumors are located. Further, thebesian veins are not peculiar to the right side of the fossa ovalis. In other parts of the body similar formations would be called hemangiomas with little argument. It is suggested that "hemangioma" or "focal vascular malformation" are more descriptive terms.

Although not a tumor, it is worth mention here that a varicosity of the coronary sinus has been reported. In a brief note, Maddox [32] described such a deformity occurring in an elderly woman. The caliber of the distended sinus was described as equal to that of the patient's aorta.

Rhabdomyoma.—The status of these interesting tumors, like that of the myxomas, has not yet been established to the general satisfaction. A host of terms has been used to describe two different conditions whose appearances overlap. A similar, confusing, term has been employed to describe a condition unrelated to this subject. Recent considerations of this group are found in the articles of Landing and Bangle [33] and of Kidder.[34] Approximately 70 of these tumors have been reported.

The largest number of cases are those in which one or several poorly defined nodules are present in the heart, usually that of a child with tuberous sclerosis. These have been diagnosed as rhabdomyoma, glycogenic tumor or congenital nodular glycogenic degeneration. Microscopically, the nodules consist of the so-called spider cells, in which the nucleus appears suspended by threads of cytoplasm passing between large vacuoles, sometimes glycogen filled. Frequently the vacuoles are not large and the cells have abundant granular cytoplasm. The tumors do not produce glycogen, and the use of the term "glycogenic" in connection with them seems poorly founded. Three cases have been reported as instances of diffuse rhabdomyoma. They are considered by Landing and Bangle to be examples of glycogen storage disease, or von Gierke's disease (glycogenosis), affecting the heart. This condition is not associated with tuberous sclerosis. The patients have a family history of glycogenosis. True "spider" cells are not present. The term "familial cardiac glycogen storage disease" has been suggested by these authors.

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32. Maddox, K.: A Case of Varicose Coronary Sinus, M. J. Australia **2**:261, 1935.

33. Landing, B. H., and Bangle, R.: Familial Cardiac Glycogen Storage Disease: Report of Two Cases and Discussion of Relation to Other Forms of Abnormal Glycogen Deposition, to be published.

34. Kidder, L. A.: Congenital Glycogenic Tumors of the Heart, Arch. Path. **49**:55-62 (Jan.) 1950.

The third term which has been used is cardiomegalia glycogenica circumscripta (circumscribed glycogenic cardiomegaly). It has been applied to degeneration of muscle fibers occurring in the hearts of several children dead of congenital heart disease. It is not an entity, and is only a well recognized degenerative phenomenon erroneously considered neoplastic.

Although rhabdomyoma is certainly a distinct entity, its status as a neoplasm is more difficult to determine. It may properly be considered a hamartomatous defect. Steinbiss [35] has shown that regression of rhabdomyoma nodules does take place. No one has demonstrated progressive enlargement of the nodules; they are not encapsulated, and rhabdomyosarcoma has not been observed arising in them. The nodules may well represent focal arrest in the maturation of cardiac muscle fibers, since in one stage of development the myocardial fibers bear a resemblance to the cells composing the nodules. This matter is discussed by Farber.[36]

Since there is reasonable doubt that the rhabdomyoma is a true neoplasm, the advisability of using the suffix -oma may be questioned. Common usage dictates primarily that it be retained, since a considerable literature exists concerning the tumors. No true rhabdomyoma has been described, either in the heart or in skeletal muscle, and no confusion is likely in this regard. Myoblastoma, if it is a muscle tumor, is quite different and would not be confused with rhabdomyoma. Finally, it is considered proper to use the term "hamartoma," and the suffix may be carried from this term to be used with these hamartomatous growths.

Rhabdomyoma of the heart may thus be considered as a hamartomatous tumor appearing in the form of nodules in the hearts of persons who often have tuberous sclerosis as well. It usually appears in children, may regress and possibly represents a focal arrest in the maturation of cardiac muscle. Diffuse rhabdomyoma has not been proved to exist, and the reported examples are probably manifestations of localized glycogenosis (glycogen storage disease).

Fibroma and Hamartoma.—These tumors may be conveniently considered together. This fact is a good commentary on the term "hamartoma," which, when taken alone, provides no information. In the heart a hamartoma may be composed of muscle, fibrous tissue, endothelium, blood vessels, fat, nerves or a combination of these elements. Some of the myxomas and lipomas, all of the rhabdomyomas and all of the angiomas could be included in this category. However, those cases reported as instances of hamartoma most closely resemble certain other cases which have been reported as instances of fibroma, and the two will be considered together here. Because of this confusion in terms it is not possible to state the exact numbers of these tumors which have been reported.

The hamartoma of Neugebauer [37] was mixed, consisting of fibromatous and lipomatous elements; his patient was a 25 year old man with a history of rheumatic fever. Symeonidis and Linzbach [38] reported three fibroelastic hamartomas in a

35. Steinbiss, W.: Zur Kenntnis der Rhabdomyome des Herzens und ihrer Beziehungen zur tuberösen Gehirnsklerose, Virchows Arch. f. path. Anat. **243**:22-38, 1923.

36 Farber, S.: Congenital Rhabdomyoma of the Heart, Am. J. Path. **7**:105-130, 1931.

37. Neugebauer, W.: Hamartom des Herzens, Zentralbl. f. allg. Path. u. path Anat. **70**:2-5, 1938.

38. Symeonidis, A., and Linzbach, A. J.: Über die fibroelastösen Hamartien des Myokards (sog. Herzfibrome), Virchows Arch. f. path. Anat. **302**:383-404, 1938.

newborn, a 15 month old child and a 53 year old man. These malformations were located, respectively, at the apex, in the posterior wall of the left ventricle and below the aortic valve. Kulka [39] reported a tumor as a fibroma and found two similar tumors described in the literature. His patient was an infant of 8 months who died suddenly. A mass of fibrous tissue was present in the anterior wall of the left ventricle. Mönckeberg's [20] article presents a picture of a fibroma closely resembling that of Kulka's patient and that of the patient described below. Wagstaffe [40] reported a case of sudden death in a 3 month old girl who had a fibroma of the interventricular septum. The sudden death occurring in the infants having this tumor is interesting, and the cause is uncertain.

One tumor has been reported as a fibrosarcoma of the heart which seems to me to fall into the category of benign developmental errors. The patient of Fidler, Kissane and Koons [23] was a 9 month old child with cleft palate, harelip and bilateral inguinal hernia, who died after a plastic operation. A hard white mass was present in the left apex and septum, involving also the left ventricle. The authors described closely packed spindle cells with poorly distinguished cytoplasm and fibrosis of the adjacent myocardium. Their published pictures show a uniform sheet of cellular fibrous tissue surrounded by less cellular, dense fibrous tissue. No mitoses, anaplasia or giant cells are mentioned. There were no metastases. The impression is that the tumor belongs with others which have been called fibroma or hamartoma.

There is a group of valvular deformities occurring in the hearts of children which Craig [41] considered as forms of congenital endocardial sclerosis. Several of these have been called myxomas or fibromyxomas. As Craig has shown, the deformities are for the most part unrelated to other anomalies or cardiac defects and probably represent a persistence of the early stage when the valve is composed entirely of myxoid tissue. The cases cited below probably are best placed in this category.

Abrahamer [42] found myxomatous thickenings of the tricuspid and pulmonary valves in a newborn girl. Helwig [43] observed a "myxoma" of a pulmonary valve cusp in a newborn which may also be an example of this condition. Similarly, Jacobssen's [44] patients presented this picture. One, a 26 day old boy, had small myxoid excrescences on each aortic cusp. The second patient was a 5½ month old girl with a cardiac septal defect and verrucous thickenings on the aortic valve cusps. The deformities in each were called "myxofibroma." Whorton, in his review of the sarcomas, cited an unpublished case considered to be an instance of hamartoma, in which there were multiple valvular defects composed of loose myxoid tissue, similar to those in the foregoing instances. These defects are directly related to more extensive, but similar, processes involving other regions of the heart, and they are too complex to be dealt with here. Craig described one form

39. Kulka, W.: Intramural Fibroma of the Heart, Am. J. Path. **25**:549-557, 1949.

40. Wagstaffe, W. W.: Fibrous Tumor of the Heart, Tr. Path. Soc. London **22**:121-124, 1871

41. Craig, J.: Congenital Endocardial Sclerosis, Bull. Internat. A. M. Mus. **30**:15-67, 1949.

42. Abrahamer, I.: Myxomatöse Bildungen an den Herzklappen beim Neugeborenen, Zentralbl. f. Gynäk. **55**:2344-2348, 1931.

43. Helwig, F. C.: Tumors of the Heart, J. Kansas M. Soc. **36**:265-272, 1935.

44. Jacobssen, E.: Two Cases of So-Called Myxofibroma of the Heart Valves, Producing Clinical Symptoms and Congenital Vitium, Ann. Pædiat. **161**:1-11, 1943.

of congenital endocardial sclerosis in which the valves alone were affected. The cases mentioned here fit well with his. The evidence indicates that they are not neoplastic, but are hamartomatous malformations.

The heart valves also give rise to a fibrous tumor which is uniform enough in the reported cases to justify separate discussion of it as "fibroma of the heart valves." At the time of Yater's review 25 cases of this tumor had been reported, and he added two of tumors of the aortic valve. Since that time Hertzog [45] has reported another case of aortic valve tumor. The heart valve fibromas appear as papillary, pedunculated, villous masses overlaid by endothelium and composed of acellular hyaline fibrous tissue. Some of the tumors have an organized system of blood vessels, while others are avascular. Bohrod's [46] case showed a prominent vascular element. Nine tumors have been found on the aortic, 9 on the tricuspid, 5 on the mitral and 5 on the pulmonary valve.

The valvular fibromas are closely related to the myxomas, and they, too, have been suspected of being non-neoplastic. In four of the reported cases signs of chronic endocarditis have been noted. Koechlin [47] felt that there were no true tumors of cardiac valves and that all these growths were either inflammatory in origin or Lambl's excrescences. Thorel shared this opinion. The inflammatory origin is not supported by the appearance of the tumors or the other findings in the patients. They are not known sequelae of vegetative valvular endocarditis in patients who have undoubtedly had that disease. Lambl's excrescences, which Koechlin referred to, are minute knoblike or villous projections of the aortic valve, averaging from 0.2 to 0.3 cm. in maximum dimension. Lambl [48] found them in 2 per cent of 1,000 autopsies. Koechlin found them in 20 per cent of 150 autopsies and is the only person to describe them as occurring on the mitral valve. He found these excrescences on two scarred mitral valves. To equate these large tumors with the minute projections described by Lambl hardly seems justified, although they may be related. Their only similarities are that they are both fibrous and occasionally occur on the same valve.

MISCELLANEOUS TUMORS

Lipomas have been reported to occur in the heart. The last review of the subject was presented by Martin [49] in 1929, at which time he found 21 recorded cases. They have been observed most frequently in subendocardial and subepicardial locations, although they have been seen intramurally. Brewis' [50] patient had a pedunculated lipoma arising from the interventricular septum which completely obstructed the tricuspid valve. As in other cases in this group, there is no mention of a microscopic examination of the tumor, a fact which makes evaluation difficult.

45 Hertzog, A. J.: Papillary Fibroma of Cardiac Valve, Arch. Path. **22**:222-224 (Aug.) 1936.

46. Bohrod, M. G.: Multiple Hemangiofibroma of the Pulmonary Valve, Arch. Path. **8**:68-77 (July) 1929.

47. Koechlin, E.: Über primäre Tumoren und papillomatöse Exkreszenzen der Herzklappen, Frankfurt. Ztschr. f. Path. **2**:295-342, 1908.

48. Lambl: Papilläre Excrescenzen an der Semilunar-Klappe der Aorta, Wien med. Wchnschr. **6**:244-247, 1856.

49. Martin, E.: De la pathogénie de certaines tumeurs du cœur: Contribution à l'étude des myxomes et des lipomes du cœur, Ann. d'anat. path. **6**:159-188, 1929.

50. Brewis, R. A.: A Case of Lipoma in the Right Ventricle of the Heart, Lancet **2**:829, 1905.

Epithelial inclusions have been found in the heart on 13 occasions. Nine of these structures have been epithelium-lined cysts of macroscopic size. The subject of these cysts was reviewed by Sachs and Angrist [51] in 1945. They, together with authors in the foreign literature, felt that such cysts may arise from sequestration or heterotopia during the period when the heart and the foregut are in close approximation. Bremer [52] feels that the separation of the heart and the foregut is too complete in man to make this explanation likely, particularly since metaplasia of mesodermal elements furnishes a more likely source of such inclusions. He feels that this explanation holds even when ciliated columnar epithelium is present.

The other epithelial tumors were microscopic. Rezek's [53] tumor of the atrium of a 71 year old woman was an incidental microscopic finding; the patient had heart block clinically. It contained epithelial-like cells and minute cysts. Rabson and Thill [54] described a case in which epithelial cells were found in the atrial wall in the plane of the mitral ring; there were no cysts. Leicher [55] described two patients, one with heart block, the other with bradycardia and Cheyne-Stokes respiration. In the region of the atrioventricular node both had small epithelial inclusions with minute cysts. He termed these "hamartomas"; this seems to be an incorrect use of the term. As commonly applied, "hamartoma" designates a tumor composed of elements normally found in the region where the tumor arises. Epithelial cells are not normally present in the heart, and the correct term for such an occurrence would be "choristoma," if one felt that it represented a developmental displacement of tissue.

TREATMENT

To discuss the subject of treatment at length is beyond the scope of this paper, but a few remarks may be based on pathological concepts and on the material presented.

Mahaim [56] has suggested that angiocardiography affords a means of demonstrating cardiac tumors during life in those cases in which intracavitary projections are of sufficient size. Since 80 per cent of the myxomas are polypoid and almost all are large when producing symptoms, it would seem that this method is feasible. Mahaim has also observed that the microscopic examination of tumor emboli would suggest the diagnosis. The value of pneumopericardiography has been once demonstrated.[22n]

Should clinical findings and angiocardiography indicate the presence of a pedunculated intra-atrial tumor, the only feasible treatment would be surgical. With artificial heart-lung preparations on the clinical horizon, and intracardiac procedures already becoming more numerous, such an attack may soon be practical. Beck has already proposed that myxomas be dealt with by the neurosurgical technic

51. Sachs, L. J., and Angrist, A.: Congenital Cyst of the Myocardium, Am. J. Path. **21**:187-193, 1945.

52. Bremer, J. L.: Personal communication to the author.

53. Rezek, P.: Über eine primäre epitheliale Geschwulst in der Gegend des Reizleitungssystems beim Menschen, Virchows Arch. f. path. Anat. **301**:305-320, 1938.

54. Rabson, E. M., and Thill, L. J.: Epithelium-like Inclusions in the Heart, Am. J. Path. **24**:655-658, 1948.

55. Leicher, F.: Zur Pathogenese der primären epithelialen Tumoren im Reizleitungssystem des Menschen, Ztschr. f. Kreislaufforsch. **37**:105-117, 1948.

56. Mahaim, I.: Nouvelles conceptions sur le traitment chirurgical du rétrécissement mitral, Cardiologia **12**:11-17, 1947.

of suction removal or by actual opening of the atrium. Reviewing the structure of myxomas, one notes that after suction removal the large vessels which some of them contain would bleed directly into the heart. This would seem innocuous, except for superimposed thrombosis.

REPORT OF CASES

The four cases described below have been encountered in an autopsy series of 4,200 cases over a period of 22 years. The incidence is thus 0.1 per cent in this laboratory.

CASE 1 (myxoma 116935).—This 69 year old white man was referred to the Overholt Thoracic Clinic because of suspected carcinoma of the lung. The past history showed "phlebitis" of the left leg, treated in France 25 years before admission, and malaria, contracted in the South Pacific 40 years before admission. Medical consultation before surgical intervention revealed as positive findings diminished breath sounds and fremitus on the right and a blood pressure of 140/85. An electrocardiogram was normal. Roentgenograms of the chest showed a centrally excavated mass in the lower lobe of the right lung, and tumor cells were present in the bronchial secretions. Right pneumonectomy was performed without incident. The removed lung contained a centrally necrotic epidermoid carcinoma in the lower lobe. On the second postoperative day right hemiplegia and aphasia developed, and death followed in 48 hours.

The major finding at autopsy was also the cause of death. Several extensive areas of hemorrhagic softening were present in both cerebral hemispheres without thrombosis.

The heart weighed 540 Gm. and presented a polypoid mass in the left atrium, arising 2.0 cm. below the rim of the anatomically patent foramen ovale (fig. 3*A*). This tumor was sessile, firm, smooth and 1.5 cm. in greatest dimension. On section it was composed of purple-red myxomatous tissue. The coronary arteries were not sclerotic, the myocardium was free of fibrosis, and the endocardium was everywhere smooth and glistening. The pericardium was normal.

Microscopically, the cardiac tumor arose from the subendocardial connective tissue, above an intact medial elastic fiber network. It consisted of vascular, poorly cellular, palely eosinophilic tissue covered by endocardium. It was uniform at all levels. Focal hemorrhages were present, and abundant hemosiderin was scattered throughout the tissue. Near one boundary of the mass adjacent to the atrial septum, was a poorly defined mass of mucoid tissue (fig. 3*B*). Perivascular lymphocytic aggregates were present in the proximal part of the structure. Several of the many capillaries were thrombosed and infiltrated by polymorphonuclear granulocytes. The scattered nuclei of the tumor tissue were ovoid, regular and free of mitoses. Their cell bodies were poorly outlined or not visible. Collagen deposition was variable. Multinucleate forms were frequent. Several thick-walled blood vessels were situated at the junction with the subendocardial tissue. Elastic fibers were focally numerous. Mucin stains were positive in one area near the proximal margin. The remainder of the myocardium and endocardium were not remarkable. There was no evidence of rheumatic fever or myocardial fibrosis.

CASE 2 (myxoma 118405).—A 71 year old woman came to the Lahey Clinic with a four month history of intermittent diarrhea and roentgen evidence of obstruction in the lower part of the sigmoid. Except for scarlet fever at age 10, without recorded complications, the history was noncontributory. Exploratory operation revealed a large mass in the lower part of the rectosigmoid, and the first stage of a Lahey resection was carried out. A mass was palpated in the gallbladder, and biopsy resulted in a diagnosis of adenocarcinoma. Postoperatively the patient's response was poor. Arrhythmias developed which were attributed to potassium depletion. Approximately 18 hours before the patient's death, one month after operation, signs of peritonitis appeared, followed quickly by collapse and death.

Autopsy revealed the immediate cause of death as peritonitis secondary to volvulus and infarction of a 120.0 cm. segment of jejunum. There was a large adenocarcinoma of the rectosigmoid, which had extended to the regional lymph nodes and metastasized to the lungs

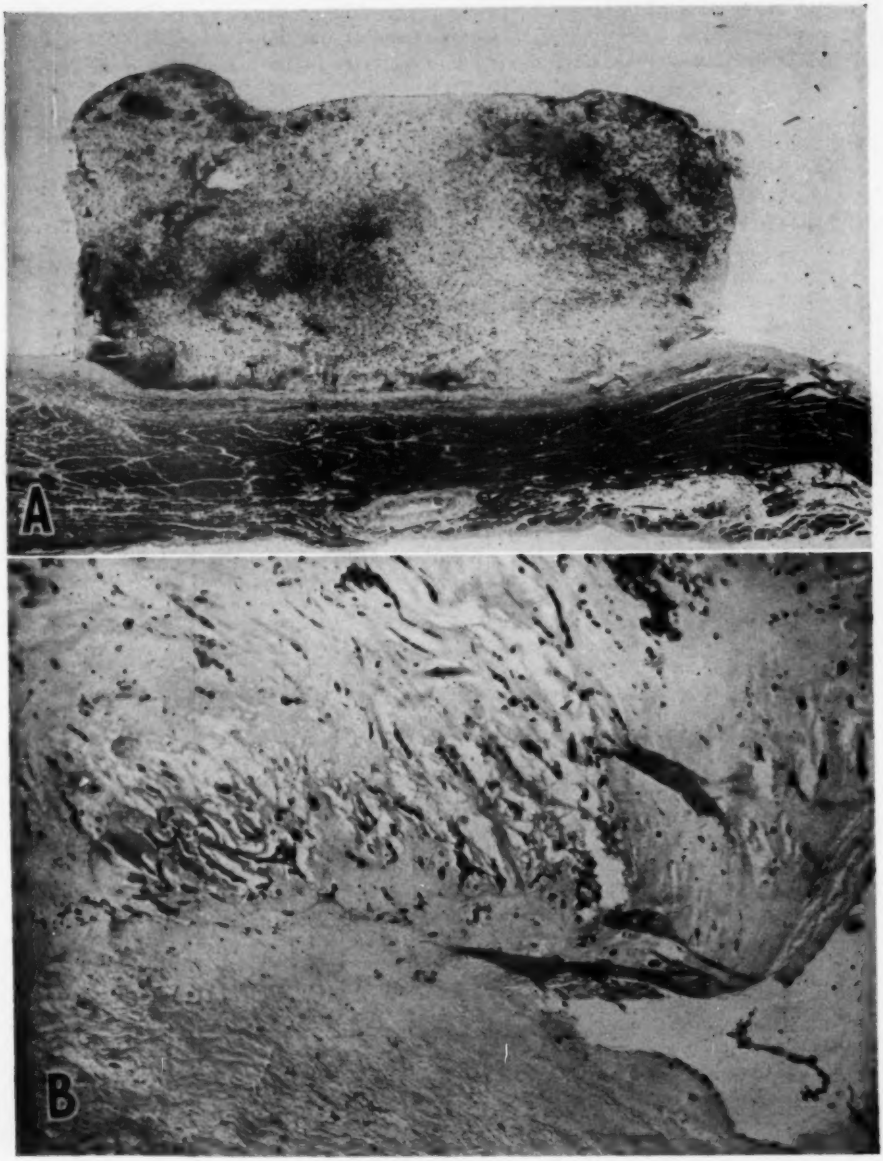


Fig. 3. (myxoma, case 1).—*A*, section through the entire growth, with scattered hemorrhages appearing as dark areas against the poorly cellular surrounding tissue; the atrial wall is otherwise unremarkable. Eosin–methylene blue; × 9.

B, section through the edge and base of the tumor, showing intact endothelium reflected from the atrial lining over the tumor, and a myxoid area extending toward the center of the tumor mass. Eosin–methylene blue; × 9.

and the liver. A second tumor was present in the gallbladder, forming a papillary mass that partially filled its lumen, and extending through the wall. Microscopically, the gallbladder tumor presented an entirely different appearance from the rectosigmoid growth, and it was diagnosed as papillary adenocarcinoma. The invasion of the gallbladder wall was slight in extent, and the metastases were felt to have come from the intestinal neoplasm.

The heart weighed 210 Gm. and was externally unremarkable. There were no pericardial adhesions. Extending into the left auricle was a smooth, dome-shaped, sessile mass 3.0 by 2.0 cm., arising from the site of the fossa ovalis. On section the structure was homogeneous and yellow-white, with focal hemorrhages. A single thrombosed blood vessel was present near the atrial septum. The remaining endocardial surfaces were smooth and glistening. There were no thrombi in any chamber. The valves were normal. The myocardium was free of scarring. The coronary arteries were patent and were free of atheromas.

Microscopically, the tumor consisted of poorly cellular, palely eosinophilic tissue with small amounts of collagen scattered throughout. A rich capillary network was present in all portions of the mass, with focal hemorrhage and hemosiderin deposition in scattered areas adjacent to these vessels. Near the base of the mass larger and thick-walled blood vessels were present (fig. 4*A*), arising from deep within the atrial wall. One large vessel contained a thrombus estimated to be less than 24 hours old. A cyst (fig. 4*B*) containing mucoid material was present in the midportion of the tumor and was partially lined by a layer of cells up to four cells in thickness. The cell outlines of this epithelium were indistinct, were not reminiscent of any adult epithelium and most closely resembled endothelial cells. The tumor cell nuclei were scattered throughout. They were ovoid, without mitosis, and formed irregular clusters. Occasional multinucleate forms were present. Elastic tissue was focally abundant. The elastic layer of the endocardium was intact, and the vessels entering the tumor were unremarkable. Mucin stains were positive in many areas, both in association with concentrations of cells and in poorly defined areas in the stroma, particularly noticeable at the base of the tumor (fig. 4*A*). The remainder of the heart was normal microscopically. There was no increase in fibrous tissue, nor vascularization of the valves and their rings.

Case 3 (myxosarcoma 121018).—A 32 year old ex–Air Force pilot was known to have tuberculosis for four years before he was referred to the Overholt Thoracic Clinic for pulmonary resection. His disease had first been noticed in the form of cervical adenitis and had later appeared in the lungs and spread there. At the time of admission here his lung lesions had stabilized. Because of extensive destruction of the lower lobe of the right lung, with cavitation, and persistence of tubercle bacilli in the sputum, resection was deemed advisable. Two years before this, at the time the patient was first admitted to a Veterans Administration hospital, a loud systolic murmur was noted over his precordium. An electrocardiogram showed only slight elevation of the S-T segments, which later disappeared. The murmur persisted, and during hospitalization the patient was seen by many consultants in regard to that finding, but no definite diagnosis was made. His physical condition was considered good enough to warrant operation. At the Overholt Thoracic Clinic the admission physical examination showed signs of a right pneumothorax, low pulse pressure (blood pressure, 105/80) and a loud, course "rub" at the apex, best heard in systole. Two days after admission right pneumonectomy was attempted, but the patient's condition became too poor for completion of the operation. Before the procedure was abandoned the segmental arteries of the upper lobe had been ligated and divided. Recovery was prompt after this procedure. Medical consultation after this first operation produced varying opinions, but the consensus was that the operation should be completed. There were no overt signs of congestive heart failure. There were a "pericardial friction rub, an apical systolic and diastolic murmur, gallop rhythm, and electrocardiographic changes consistent with cor pulmonale." Venous pressure was 110 mm. of water in the left arm. On slight exertion the heart sounds became "tumultuous." The second operation proceeded uneventfully until the chest wall was being closed, at which time the patient succumbed despite efforts at resuscitation. At the time the pulmonary artery was ligated, the tie on the distal portion came off, and it was noted that no back bleeding occurred. The lumen was investigated and was filled with "gelatinous" material. Similar material was aspirated from the proximal pulmonary artery during the efforts at resuscitation.

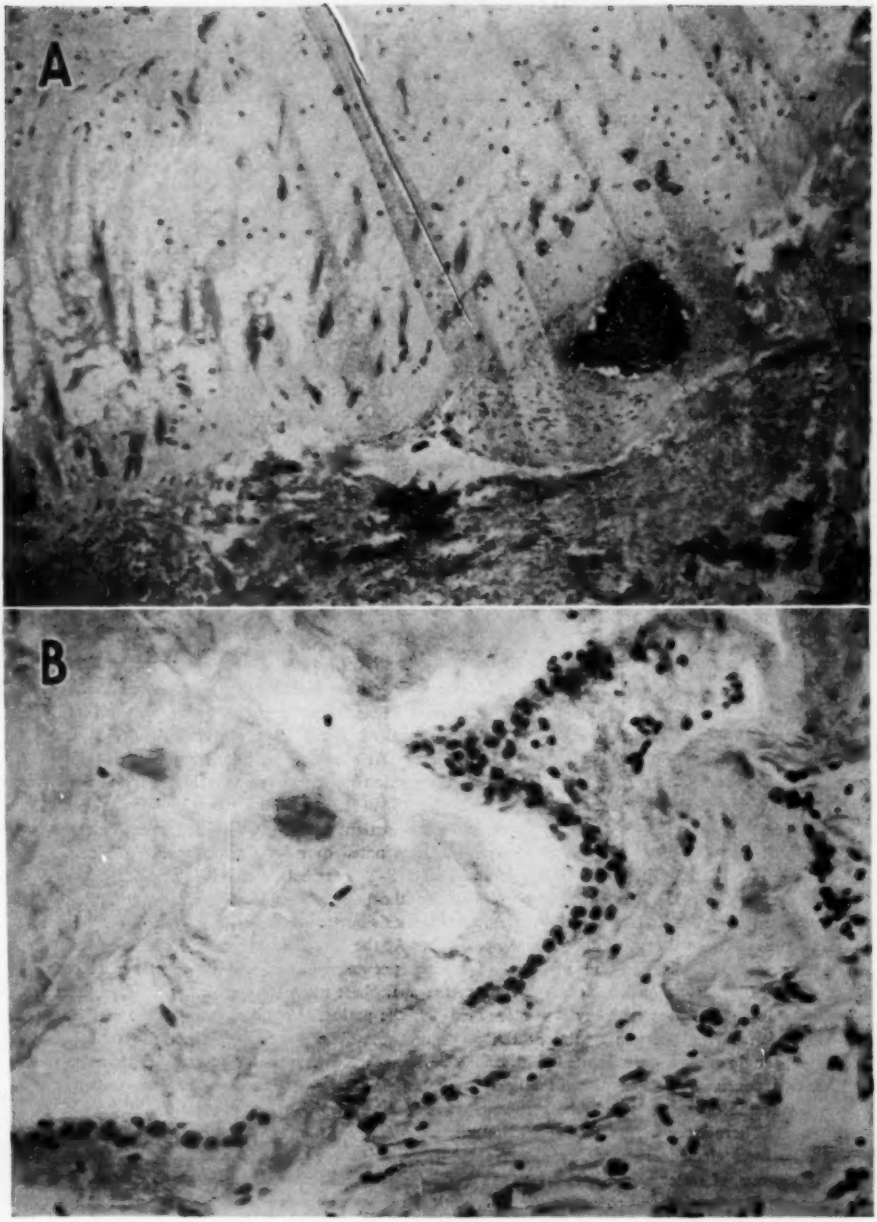


Fig. 4 (myxoma, case 2).—*A*, base of the tumor showing a large blood vessel between the myxoid tissue and the underlying atrial wall. There is slight lymphocytic infiltration around the blood vessels. × 106.

B, section through the tumor near the free border, passing through a cyst filled with mucin-positive material (left half). The lining of the cyst is incomplete and consists of poorly outlined cells suggesting an endothelial origin. Hematoxylin and eosin; × 296.

Fig. 5 (myxosarcoma, case 3).—*A*, soft, friable tumor tissue, with artefactually created villous borders, shown astride the free edge of the posterior leaflet of the tricuspid valve. The mottled cut surface is easily seen. Note fragments of tumor tissue adherent to the ventricular wall at the lower right of the picture.

B, lobar artery of the lower lobe of the left lung held open to show mass of myxoid tumor tissue filling the major portion of its lumen. Note extension of tumor tissue into segmental artery arising in midportion of picture.

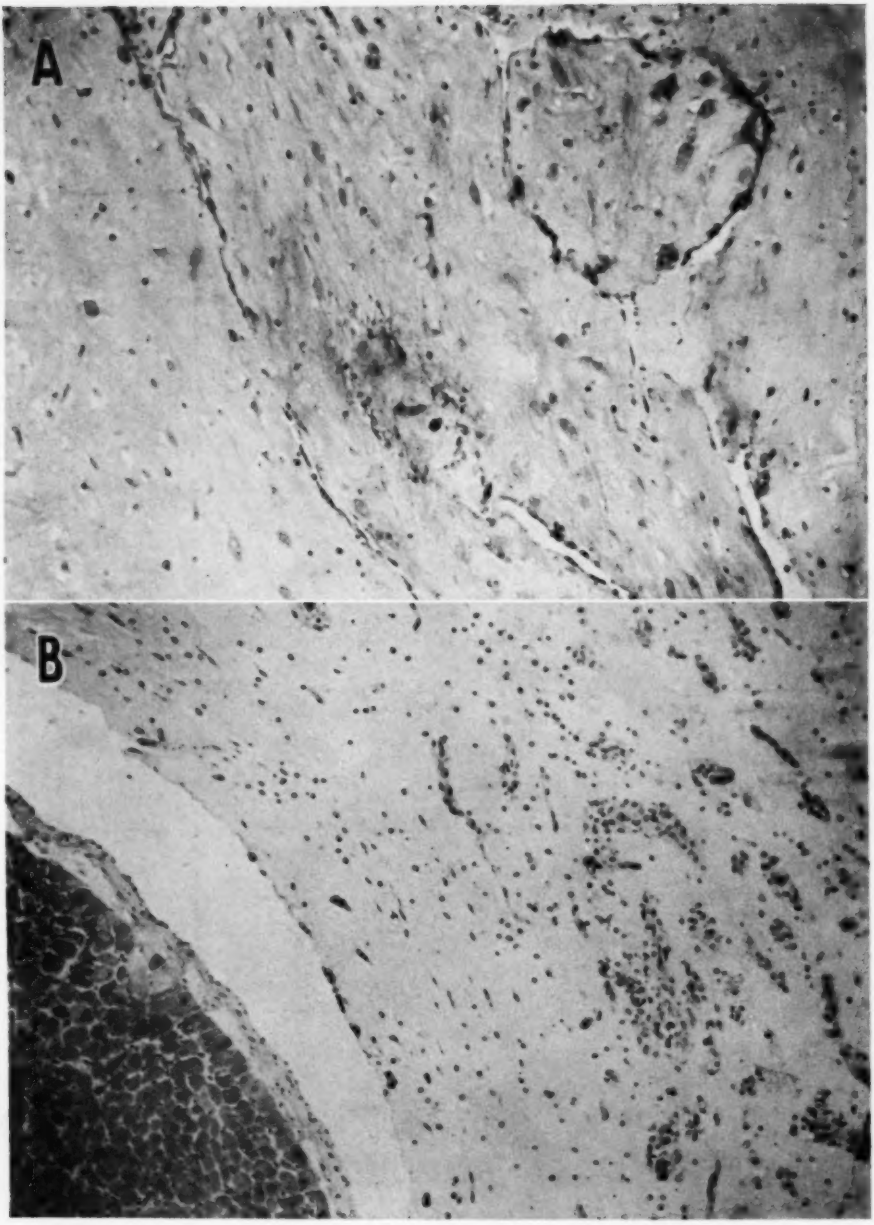


Fig. 6 (myxosarcoma, case 3).—*A*, area of loose, myxoid tissue with large, occasionally stellate cells. Mucin stains were positive. Eosin-methylene blue; × 106.

B, portion of the tumor adjacent to the ventricular myocardium, showing sparsely cellular, mucin-positive stroma with foci of thick-walled capillaries. Eosin-methylene blue; × 106.

Autopsy findings consisted chiefly in pulmonary tuberculosis and a tumor of the heart. Both lungs contained tuberculous lesions, with the principal involvement on the right, where there was extensive disease.

The heart weighed 380 Gm. The entire right ventricle was filled with mucoid, gelatinous, friable, yellow-pink material and admixed blood clot. This material extended through the pulmonary valve into both branches of the pulmonary artery (fig. 3*B*), occupying a large part of their lumens. When the bulk of the mucoid material was removed, a friable, papillary tumor was found on the posterior leaflet of the tricuspid valve (fig. 3*A*). It was approximately 3.0 cm. in maximum dimension, but its borders were artificially created by removal of the mucoid material from the ventricle. Section through the mass showed firm pink-white tissue extending from the substance of the valve leaflet, astride its free edge. Sections through both the surgically removed lung and the opposite lung revealed myxoid tissue extending as far as scattered segmental arteries. The remainder of the heart was grossly normal. The pericardium was normal, and no excess fluid was present.

Microscopically, the cardiac tumor consisted of a branched, vaguely outlined mass of hemorrhagic, poorly cellular tissue blending with the valve. Hemosiderin was deposited in many places throughout. Areas of mucinous tissue were present in all sections (fig. 4*A*). A section of the tissue filling the ventricle at a point distant from the valve had the same structure as the proximal tumor (fig. 6*B*). The interstices were filled with clotted blood. Focal lymphocytic infiltration was present. The cells composing the tumor were similar to those of the myxomas previously described; there were no mitoses. There was scattered collagen deposition. The endocardial covering was incomplete. Numerous thick-walled vascular channels penetrated the base of the valve and extended into the tumor (fig. 5*A*), which was richly vascularized, by both capillaries and small arteries. Elastic tissue was focally abundant. Mucin stains were positive in many areas throughout the tumor. Tissue identical with that composing the tumor was present in the arterial trees of both lungs and was attached to the intima of a lobar artery in each lung. The tumor tissue extended into the subendothelial layer of several vessels (fig. 7*B*).

Case 4 (hemangioma 121249).—This 38 year old white man was referred to the Overholt Thoracic Clinic for pulmonary resection. He was known to have cavitary tuberculosis for five years, and previously had had a right pneumothorax and a four stage thoracoplasty. His sputum remained positive for tubercle bacilli. Bronchoscopic examination revealed endobronchial tuberculosis, and bronchograms showed early bronchiectasis on the right. The past history revealed the usual childhood diseases and questionable rheumatic fever eight years before admission with no definite diagnosis or known sequelae. Positive findings on admission physical examination were thoracoplasty deformity of the right side of the chest, blood pressure of 160/100 and nasal polyps.

Right pneumonectomy was performed five days after admission, without incident. On the second postoperative day dyspnea developed, together with sore throat and low grade fever. On the fourth postoperative day the patient died while tracheal aspiration was being carried out to rid him of troublesome bronchial secretions.

Autopsy revealed bronchopneumonia of the remaining lung as the immediate cause of death.

The heart weighed 310 Gm. It was entirely normal except for a cluster of small polypoid excrescences along the superior rim of the foramen ovale in the right atrium. The foramen was anatomically patent. In the center of the cluster were two smooth, yellow, roughly hemispherical projections, 0.6 cm. in diameter. One of these was calcified, and the other was firm and fibrous. Adjacent to these two structures were several soft, wrinkled, red, polypoid masses from 0.2 to 0.5 cm. in length (fig. 6).

Microscopically, the structure was a cavernous angioma. Blood-filled spaces occupied a small area of subendocardial tissue beneath the intracavitary projections (fig. 7*A*). The smooth central structures were vascular spaces containing organized thrombi, one of which was calcified (fig. 7*B*). The vascular spaces varied in size from that of a capillary to that of a small vein. The endothelial lining of these spaces was regular. Scattered lymphocytes were present in the connective tissue about the vessels.

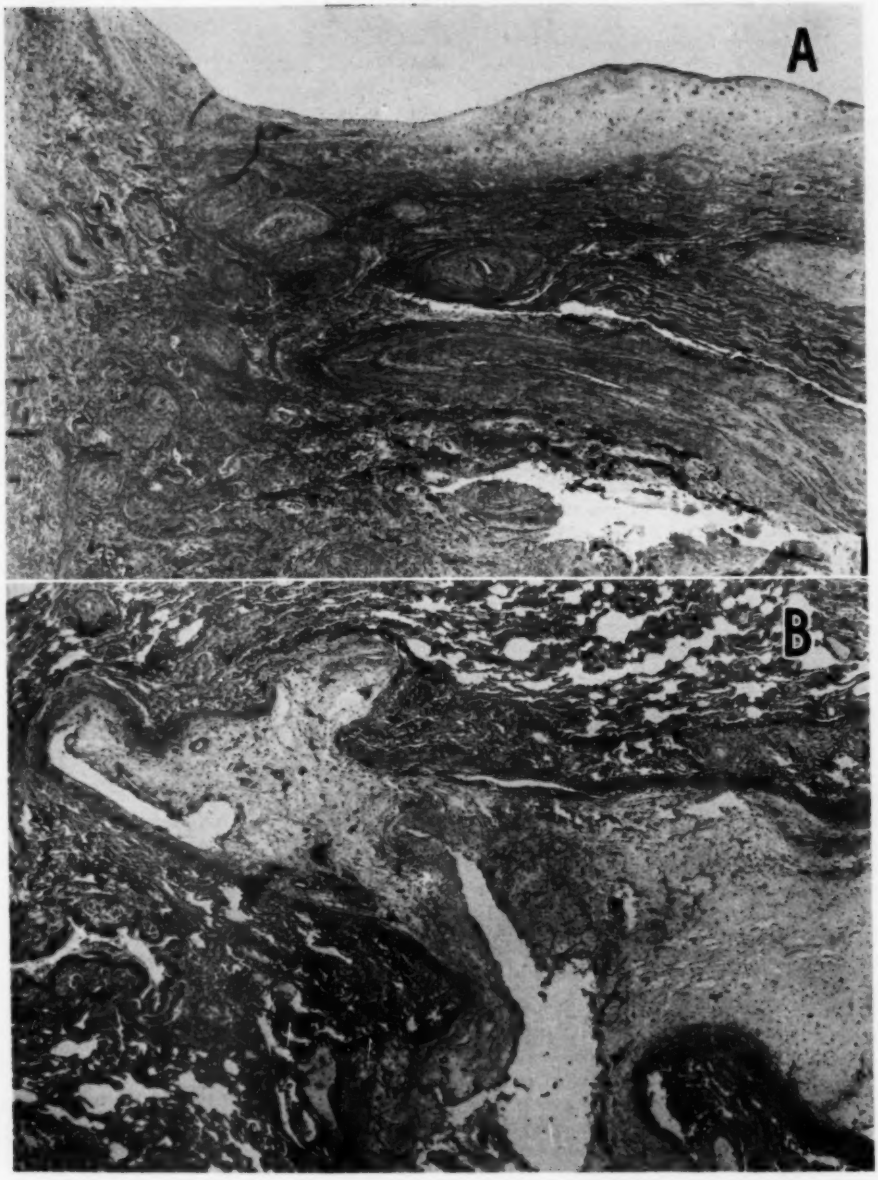


Fig. 7 (myxosarcoma, case 3).—*A*, section through the base of the tumor-bearing valve leaflet, with fragments of the growth visible at the lower right. Myocardium of the right ventricle is at the left. The entire base of the valve and its midportion are invaded by large, thick-walled blood vessels, which extend into the tumor at the lower border of the picture. Eosin–methylene blue; × 29.6.

B, section through a branch of a segmental artery of the lower lobe of the left lung, which is filled with myxoid tissue. In a few places the tumor tissue is invading the vessel wall. Note capillary spaces in the myxoid tissue. Eosin–methylene blue; × 29.6.

Fig. 8 (hemangioma, case 4).—A cluster of smooth and wrinkled excrescences bulge beneath the endocardium of the superior rim of the foramen ovale in the right atrium. Approximately × 3.

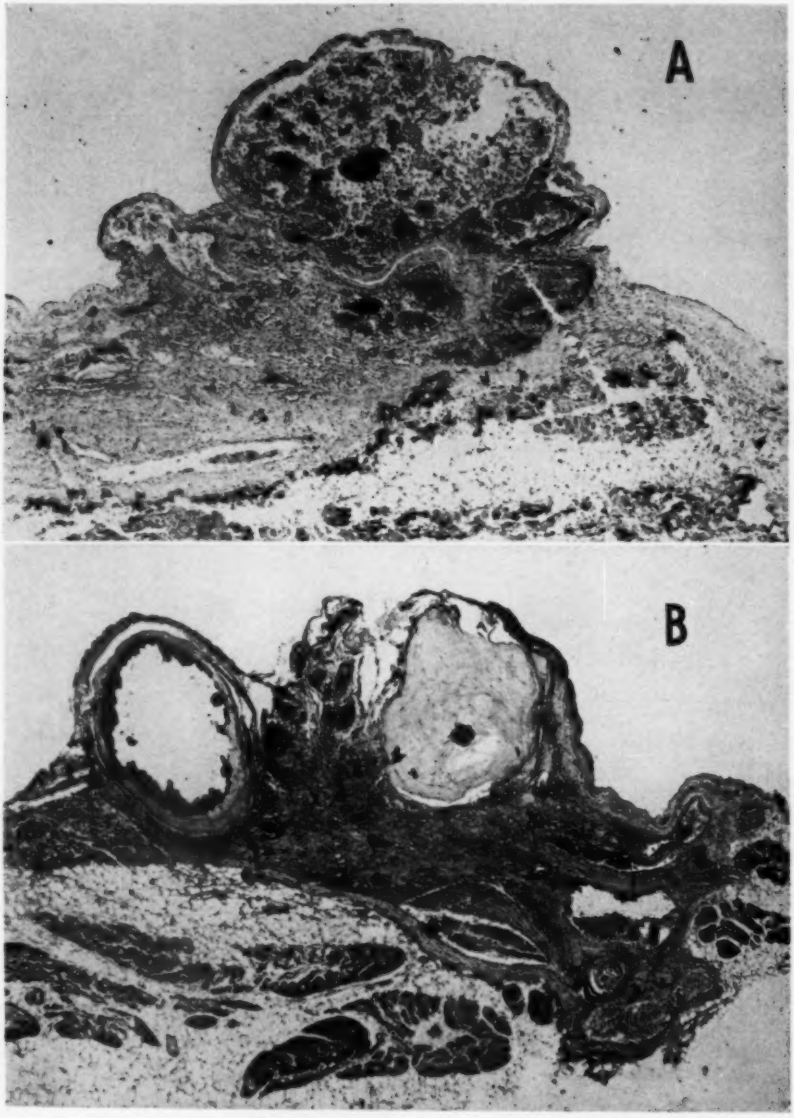


Fig. 9 (hemangioma, case 4).—*A*, cluster of thin-walled, blood-filled spaces bulging through the endocardium and extending through the full thickness of the interatrial septum. Grossly, these appear as the wrinkled, soft, polypoid excrescences seen in figure 8. Hematoxylin and eosin stain; × 38.5.

B, section passing through large, smooth nodules shown in figure 8. The atrial surface is seen at the top of the photograph. The lumen at the right is filled with a fibrous, organized thrombus. The lumen at the left contains fragments of a phlebolith. The intervening tissue consists of thin-walled vascular spaces; similar spaces are scattered through the surrounding tissue of the auricular septum. Small veins are seen at the lower right. Hematoxylin and eosin stain; × 27.

TABLE 3.—*Summary of Information Concerning Tumors of the Heart*

Type of Tumor	Approximate Number Reported	Clinical Features	Diagnosed During Life	Location in Heart	Pathological Features		Pertinent References
					Gross	Microscopic	
Metastatic	500 +	Usually silent, but may interfere with conduction system; rarely produces heart failure	Yes, approx. 20 times	Anywhere; right side oftener than left	Nodules similar to those of metastatic tumor elsewhere; rarely implants on valves; rarely lymphangitis	Similar to primary growth	1; 4-9
Myxoma	125 ±	Symptoms of mitral stenosis, occasionally influenced by position; rarely simulates endocarditis	No	Atriums, usually left, near fossa ovalis	Soft, smooth, globoid or dome-shaped, white to brown mass, often pedunculated	Poorly cellular, loose tissue; varying vascularity; mucinous areas; pigment	1; 2; 14a-13b; 18; 19; 20; 21
Sarcoma	112	Relentless cardiac failure; occasional sudden death; rapid change in roentgenographic contour; variable ECG findings	Yes, 5 times	All over; more frequent on right	Infiltrating, or large masses replacing muscle; rarely pedunculated	Usually a "spindle cell" variant; "round cell" and rhabdomyosarcoma, also	2; 3; 22a-22m; 24-28
Angioma	46	Majority are symptomless; several have produced heart block and sudden death	No	Majority of silent ones on rim of foramen ovale; others in septums	"Varix" type—red or white, sessile or polypoid excrescences; others may not be seen grossly	Endothelium-lined spaces filled with blood, lymph and occasional thrombi showing varying organization	29a-29k; 30; 31; 32
Rhabdomyoma	70	Usually are incidental findings; occur in 50% of patients with tuberous sclerosis; most occur in children	No	Usually in ventricles	Single or multiple nonencapsulated nodules	Nodules of "spider cells"—nucleus appears suspended by threads of cytoplasm between vacuoles	33-36
Fibroma and Hamartoma							
Hamartomatous fibroma	?	Usually silent, but some have been associated with sudden death	No	Usually in ventricles	Firm, white nodule, unencapsulated	Fibrous tissue with varying amounts of fat, elastic tissue and blood vessels	23; 37-40
Valvular form of congenital endocardial sclerosis	?	Usually in infants with no other congenital defects	No	Valves, aortic most frequently	Thickening of one or more valve cusps	Loose myxomatous tissue thickening the valve	2; 41-44
Fibroma of heart valves	28	None have been described; tumor usually an incidental finding	No	Valves, aortic most frequently	Villous, pedunculated fibrous mass	Acellular hyaline tissue covered with endothelium	1; 43-48
Miscellaneous							
Lipoma	21	At least one has produced valvular insufficiency; probably variants of myxomas or hamartomas	No	Anywhere	Sessile or pedunculated fatty masses	Fat	49
Epithelial inclusions	13	Three have been associated with conduction defects	No	Myocardium, principally left ventricle and interatrial septum	Small cyst; one case, as thickening of interatrial septum	Cyst lined with flat or columnar epithelium; small epithelial clusters with cystic spaces	51; 53-55

SUMMARY AND CONCLUSIONS

The information collected concerning tumors of the heart is summarized in table 3.

Although admittedly rare, tumors of the heart are frequent enough and important enough to deserve the attention of pathologists and cardiologists, in the hope that they may some day be added to the growing list of curable forms of heart disease.

Metastatic tumors of the heart are not uncommon in people dying of cancer, and they come from a wide variety of primary sites. Their pathogenesis is discussed in the light of the peculiarities of the heart's vascular system and constant activity. A summary of the pathologic features of 146 metastatic heart tumors from this laboratory is presented.

The myxoma is considered to be a true neoplasm and its pathogenesis is discussed. It commonly takes origin from the region of the foramen ovale, and this is considered due to the presence there of most of the heart's connective tissue and possibly to endocardial deformities, which occasionally are found in the region. The usual myxoid appearance of these tumors may be due to the mechanical stress to which they are subjected.

The sarcomas reported in the literature number 112 at the present time (1950). They are briefly discussed, and reasons for their rarity are considered.

Rhabdomyoma is briefly discussed, and an attempt is made to resolve some confusions of terms which have arisen.

Angiomas are few, and some have produced complete heart block. The varices of the German literature are probably best included in this category.

Fibromas and hamartomas are considered together, and several patterns of growth reported under various headings in the literature are grouped in this classification.

Miscellaneous tumors are listed with brief comment.

Certain pathologic aspects of treatment are briefly presented.

Four primary tumors are reported, two myxomas, one myxosarcoma and one angioma.

Drs. Richard H. Overholt and Francis M. Woods, of the Overholt Thoracic Clinic, gave me permission to use cases 1, 3 and 4; Dr. Richard B. Cattell, of the Lahey Clinic, gave me permission to use case 2. Mr. Sherman Atwell, of the Overholt Thoracic Clinic, made the photographs reproduced in figures 5 and 8. Advice and suggestions were contributed by Drs. Shields Warren, William A. Meissner and Samuel P. Hicks.

Notes and News

Announcements by the American Board of Pathology.—At a recent meeting of the Board of Trustees of the American Board of Pathology Drs. James B. McNaught, A. S. Giordano and William B. Wartman were elected members of the Board of Trustees. Drs. McNaught and Giordano were nominated by the American Society of Clinical Pathologists and Dr. Wartman was elected as a member-at-large and as assistant secretary of the Board.

Officers of the Board elected were Dr. N. Chandler Foot, of New York, president; Dr. James B. McNaught, of Denver, vice president; Dr. Robert A. Moore, of St. Louis, secretary-treasurer.

The next examination of the American Board of Pathology will be held in Cleveland, at the Institute of Pathology of Western Reserve University on Monday and Tuesday, April 23 and 24, 1951.

In view of the present emergency situation, the Board approved awarding of credit for time in the Armed Forces on the following basis:

"In view of the national emergency the American Board of Pathology will, as of July 1, 1950, accept time spent by commissioned personnel in the government service for credit toward the Board's requirements. Each request for credit will be judged on an individual basis except that in no instance will more than two of the three years of required supervised training be so credited. This policy will remain in effect for an indefinite period and notice of cancellation of it will be given at least one year in advance."

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

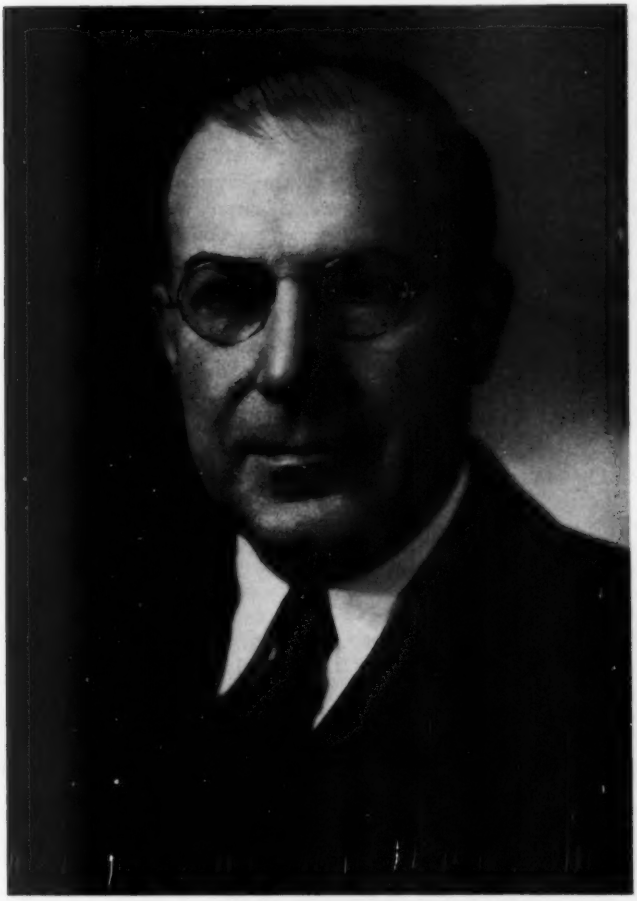
Obituary

WILLIAM F. PETERSEN, M.D.

1887-1950

William F. Petersen, emeritus professor of pathology at the University of Illinois College of Medicine, died Aug. 20, 1950. He was born in Chicago, March 25, 1887. He attended the Armour Institute of Technology, was graduated from the University of Chicago and in 1912 received his M.D. degree from Rush Medical College. After doing graduate work in biochemistry and pathology at Harvard and Columbia universities, he was appointed assistant professor of experimental medicine and pathology at Vanderbilt University. During World War I he served in the Medical Corps of the United States Army. In 1919 he married Alma Schmidt, daughter of Dr. Otto L. Schmidt, physician and historian. In 1919 Dr. Petersen joined the faculty of the University of Illinois College of Medicine. As professor of pathology from 1924 to 1942, he carried on extensive research and published more than 200 articles in various scientific journals in the United States and Europe and was the author of "Protein Therapy and Non-specific Reactions," "The Patient and the Weather" (monographs with Margaret E. Milliken, 5 volumes), "Lincoln and Douglas," "The Weather as Destiny," "Hippocratic Wisdom" and "Man, Weather, and Sun." He was a pioneer investigator of the effect of weather on disease and on the normal population.

Dr. Petersen at one time was attending pathologist at the Cook County Hospital and at the time of his death he was director of clinical research at St. Luke's Hospital in Chicago. He was a member of numerous scientific societies, including the American Association of Pathologists and Bacteriologists, the American Association for Physical Anthropology, the American Academy of Applied Nutrition, and the Illinois State Historical Society, and governing honorary life member of the Chicago Historical Society; he was an Honorary Fellow of the American College of Allergists, the Chicago Pathological Society (former president), the Chicago Society for Internal Medicine, the American Society for Experimental Pathology (former president) and the Chicago Literary Club. He served on the advisory committee of the Chicago Board of Health; he was instrumental in the planning of



WILLIAM F. PETERSEN, M.D.
1887-1950

a Chicago and Cook County health survey of the United States Public Health Service. For many years he was chairman of the Board of Governors of the Institute of Medicine, Chicago.

On Aug. 7, 1950, while at work in his garden in Lake Geneva, Wis., he was suddenly stricken with a cerebral hemorrhage and died Aug. 20, 1950. Dr. Petersen was a remarkable man who endeared himself to all with whom he had contact. He personified the true physician and investigator. He was a kindly and trusted adviser and enjoyed the friendship and respect of a wide circle of students, teachers and investigators in the field of medical science. He is survived by his widow and three sons, Eduard (physician), Conrad and William.

S. A. LEVINSON.

Books Received

KLINISCHE PATHOLOGIE DER BLUTKRANKHEITEN. By Prof. Dr. Rudolf Schoen, director of the University Medical Clinic in Göttingen, Germany, and Prof. Dr. Walter Tischendorf, superintendent of the University Medical Clinic in Göttingen. Price, 57 German marks. Pp. 521, with 101 illustrations. George Thieme Verlag, Diemershaldenstrasse 47, Stuttgart-O, 1950.

The authors of this monograph are internists with special interest in diseases of the blood. Tischendorf is well known as a contributor of merit to hematologic literature. The emphasis is on disturbed function, on general basic principles and on the pathogenesis of diseases of the blood. It is not a textbook of hematology in the usual limiting sense. Morphologic aspects of the subject are very much in the background, and laboratory technic is presented only as needed for correlation. On the other hand, much of what is discussed is of special interest to the clinical pathologist.

The ten major divisions cover morphology and embryology (46 pages); physiology (37 pages); technical methods, including blood count, special tests, blood grouping, study of marrow (all on 22 pages); anemia, an excellent and exhaustive discussion (136 pages); myeloid insufficiency (24 pages); hemorrhagic diseases (39 pages); the role of the spleen in diseases of the blood (a brief tabular review); leukemias and neoplasms, a stimulating chapter (82 pages); leukemoid reactions (a brief chapter), and hereditary transmission of blood disorders (a brief chapter).

There is ample evidence of the authors' profound erudition, with only occasional lapses or possibly intentional omissions. The latter probably underlies the uneven treatment of some subjects. For example, infectious mononucleosis is discussed with a few casual sentences, and the serologic tests are not mentioned at all.

The discussion of some topics, for example, blood groups and Rh factors, is inadequate and in places even erroneous: the term "isoagglutinins" is used instead of isoagglutinogens (page 150); agglutination thrombi in the blood vessels of the liver and brain are offered as the cause of icterus gravis, a view generally abandoned; prognostic application of antibody titers of the blood of mothers of erythroblastotic fetuses is spoken of as a distant possibility; anti-M and anti-N agglutinins are blamed for frequent transfusion reactions.

These and similar other defects are regrettable. They detract from an otherwise excellent monograph.

The illustrations are far below the level we have been accustomed to find in books on hematology during the last twenty years.

There are abundant bibliographic references at the end of each chapter, mainly to German publications. References to pertinent literature in other languages are few and unevenly selected. Lack of familiarity with American and British publications of the last eight years explains the previously mentioned defects.

In spite of the foregoing criticism, the book is a major contribution to hematologic literature, mainly as a source of information concerning the present day currents of thought in German hematologic circles.

BREAST DEFORMITIES AND THEIR REPAIR. By Jacques W. Maliniac, M.D., Clinical professor of plastic reparative surgery and associate attending plastic reparative surgeon, New York Polyclinic Medical School and Hospital, New York; attending plastic surgeon, Sydenham Hospital. Specialist certified by the American Board of Plastic Surgery. Pp. 193, with 119 illustrations. Price $10. Grune & Stratton, Inc., 381 Fourth Ave., New York, 1950.

MENSTRUATION AND ITS DISORDERS: PROCEEDINGS OF A CONFERENCE HELD UNDER THE AUSPICES OF THE NATIONAL COMMITTEE ON MATERNAL HEALTH. Edited by Earl T. Engle. Pp. 350, with 105 illustrations. Price $6.50. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

This volume is a record of the proceedings of a conference on menstruation, sponsored by the National Committee on Maternal Health. The first three pages review basic cytochemical studies. Atkinson correlates the increased alkaline phosphatase content of endometrial glands with the estrogenic phase of the cycle. Wislocki and his co-workers report on their extensive studies of the human cervix, indicating the presence of acid and alkaline glycerophosphatases in surface and glandular epithelium of the nonsenile endocervix and in areas of erosion and lipoidal particles in some mucus-secreting cells and scattered surface ciliated cells of the endocervix. Gomori describes his procedure for demonstrating lipases, indicating its possible use in more intensive studies of the female genital tract.

There are two papers dealing with the supply and flow of blood to the endometrium. Okkels of Denmark describes arteriovenous anastomoses in the endometrium and the nerve supply to the basal portions of the spiral arterioles. Markee has found that the blood flowing through intraocular endometrial transplants shows an increase of rate induced by estrogen, and applies this observation to the sequence of changes leading to menstruation.

The Smiths, in two papers, describe their studies on menstrual toxin, its relationship to necrosis and the possible clinical applications of these studies to menstrual disturbances and the toxemias of pregnancy. Shorr and Zweifach discuss their classic experiments on shock with the finding of vasodilatory substances in the liver under anoxic conditions and of vasoexcitatory substances in the anoxic kidney. In what way these findings can be applied to an understanding of the toxemias of pregnancy remains to be determined. The interesting studies of uterine motility performed at the University of Georgia are reported on by Woodbury. R. K. Meyer and McShan describe the changes in enzyme content of rat corpora lutea during the reproductive cycle.

Lastly, there are three papers of particular interest to the pathologist. The classic studies of Hertig and Rock concerning abortive human ova are brought up to date and, as usual, handsomely illustrated. TeLinde's observations on the endometrium in conjunction with observations on functional bleeding are particularly illuminating, as are Buxton's findings of the atypical secretory phase.

While, of necessity, these various contributions do not interdigitate and integrate in a manner substantial enough to give one a clear idea of the sequences underlying the human menstrual cycle and the related problems of disturbances in menstruation, they do indicate how much members of the medical profession have to learn about these mechanisms before order and clear thought can be brought to bear on this important subject. This is a volume that should be read by everyone interested in gynecologic pathology.

ATLAS OF TUMOR PATHOLOGY. Prepared at the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council.

TUMORS OF THE PERIPHERAL NERVOUS SYSTEM (SECTION II—FASCICLE 6). By Arthur Purdy Stout, M.D., professor of surgery, Columbia University, College of Physicians and Surgeons, New York. Pp. 57, with 56 illustrations. Price $0.60. American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C., 1949.

This fascicle on tumors of the peripheral nervous system is the first of 39 to be published concerning tumors of various organs. With it is provided an introduction

and an index for the entire series to follow. This ambitious index, jointly sponsored and supported by six organizations, will have over 30 authors. The stated purposes of the atlas include attempts to standardize and simplify nomenclature of tumors and to aid teaching of oncology. The atlas will illustrate the usual patterns of tumors of each organ and their variants, and give in text the outstanding characteristics of each. The fascicles are printed in loose-leaf form to facilitate binding in correct sequence and aid in inserting improvements. Subsequent fascicles will be briefly reviewed as they are published.

The present fascicle, or chapter, written by Dr. Stout is an auspicious debut for the atlas. Few subjects in the classification of tumors could have been chosen which are more controversial than this. The first objective of the atlas, namely, the standardization of nomenclature, is thus at once put to a severe test. If unanimity of acceptance is not achieved it will not be due to lack of scholarship and forthrightness of the author but to the complexity of the problems, the scarcity of definitive scientific answers and the lack of adequate space.

Atlases must be brief. Where noncontroversial objective matter is presented, as, for example, in geographic maps, this is no handicap but an asset. In presenting controversial and subjective material, however, brevity may be a serious handicap, as is shown by the present instance. The author divides the common tumors of peripheral nerves into two main groups, neurilemmomas and neurofibromas. He does not use enough space, pictorial or textual, to present the data to justify this classification convincingly. No essential difference is evident between figures 12 and 25, although in the text and in other illustrations points of difference between the two types are made. The author's previous publications have given more evidence.

This defect inherent in the atlas method shows why longer books cannot be dispensed with for presenting subjects which are in a state of flux. Despite disagreements, it would be desirable if authors writing on this subject in the future would adhere to the present nomenclature unless they give good evidence for not so doing. As it stands the fascicle is a beautifully illustrated, brief but clearly written description of these tumors. It sets a high standard for authors of other fascicles which, if it is achieved, assures a hearty reception for the entire atlas.

THE PATHOLOGY OF INTERNAL DISEASES. By William Boyd, M.D., Dipl. Psychl., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.C.S. (Canada), LL.D. (Sask.), D.Sc. (Man.), M.D. (Oslo), F.R.S. (Canada), professor of pathology and bacteriology in the University of Toronto, Toronto. Pp. 866, with 391 illustrations and 11 plates in color. Fifth edition. Price $11. Lea & Febiger, 600 S. Washington Square, Philadelphia 6, 1950.

This thoroughly revised fifth edition retains all the features that have contributed to the success of the previous editions of this classic work on the pathological physiology of internal disease and the mechanics of symptoms. Besides the new chapter on diseases of the bones and joints, there are added sections on renal anoxia, diffuse collagen disease, congenital hemolytic disease (Rh factor), myeloid metaplasia, splenic neutropenia and the LE cell of acute disseminated lupus erythematosus. Other subjects added for the first time and presented clearly, with admirable condensation of much valuable material, include Loeffler's pneumonia, temporal arteritis, anthracosilicosis, pulmonary moniliasis, the relation of the kidney to hypertension, renal lesions in diabetes, cortisone in rheumatoid arthritis, and choline deficiency in hypertension. Among the subjects that have been rewritten and the information brought up to date are hepatitis and cirrhosis, Cushing's syndrome, multiple myeloma, emphysema and pulmonary tuberculosis. In addition three color plates and 42 black and white illustrations have been added.

The material is well organized, and the printing is excellent. The correlated anatomic, histological and physiological approach to the pathology of disease makes the book invaluable to the clinician, the surgeon, the pathologist and others concerned with the pathology of internal diseases.

ON THE EXPERIMENTAL MORPHOLOGY OF THE ADRENAL CORTEX. By Hans Selye, M.D., Ph.D., D.Sc., F.R.S.(C.), professor and director of the Institute of Experimental Medicine and Surgery, University of Montreal, and Helen Stone, B.Sc., Institute of Experimental Medicine and Surgery, University of Montreal, Canada. Pp. 105, with 62 illustrations and 7 tables. Price $2.25. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

THORACIC SURGERY. By Richard H. Sweet, M.D., associate clinical professor of surgery, Harvard University Medical School. Pp. 345, with 155 illustrations. Price $10. W. B. Saunders Co., 218 W. Washington Square, Philadelphia 5, and 7 Grape St., London, W.C. 2, 1950.

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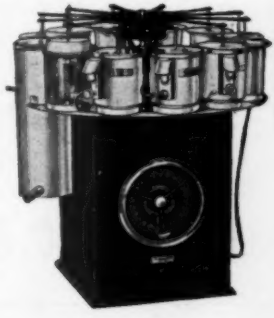

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